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INFLAMMATORY ARTHRITIS AND PREGNANCY

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Stockholm 2021

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Published by Karolinska Institutet.
Printed by Universitetsservice US-AB, 2021

ISBN 978-91-8016-113-8
Cover illustration: Sagrada Familia in Barcelona, Spain. Photo by Niklas Mattsson.

Inflammatory arthritis and pregnancy

THESIS FOR DOCTORAL DEGREE (Ph.D.)

By

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The thesis will be publicly defended in Skandiasalen, Astrid Lindgrens barnsjukhus, Karolinska University Hospital Solna on 5 February 2021 at 09:00.

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“Everything should be made as simple as possible, but no simpler”

Compressed version of a quote from Albert Einstein

POPULAR SCIENCE SUMMARY OF THE THESIS

During pregnancy, diseases and conditions can affect the health of the woman and foetus. My interest, and what we have studied, is how rheumatic conditions affect pregnancies. One rheumatic condition is arthritis, which is characterised by inflammation of the joints. Arthritis is a rare condition, so it can be an advantage to study this via national registers instead of in real life. Otherwise, it would take too long to gather enough information to draw conclusions. In this thesis, two arthritis conditions were studied: juvenile idiopathic arthritis (JIA), which is the most common childhood rheumatic disease, and psoriatic arthritis (PsA). We collected information on these conditions from population-based, nationwide Swedish registers and from a rheumatology quality register which contains more detailed clinical information about patients' disease. The personal identity number enables linkage between these registers. Data is anonymised and an ethical permit is needed.

In study I, we examined if there were more complications in pregnancies and births where the woman had a diagnosis of JIA before pregnancy, compared to pregnancies in women without such diagnosis. There were increased risks of complications in JIA pregnancies, including preterm birth (birth before 37 weeks of pregnancy), a baby born small for its age, pre-eclampsia (a hypertensive disease confined to pregnancy) and caesarean delivery.

In study II, we studied if pregnancies in women with PsA had increased risks of complications compared to pregnancies in women without PsA. In this study, we also used registers to identify pregnancies with PsA and variables that describe pregnancy outcomes. Compared to non-PsA pregnancies, PsA pregnancies had increased risks of preterm delivery and caesarean delivery. These associations were influenced by whether it was the first or subsequent pregnancy in a woman, with first pregnancies having the highest risks.

In study III, we continued to study PsA pregnancies compared to non-PsA pregnancies, and we wanted to find out if a more severe PsA disease was more prone to complications than a mild disease. We used treatment with different antirheumatic drugs as a proxy for PsA disease severity. We considered pregnancies with no treatment as mild and those with multiple drugs or treatment throughout pregnancy as more severe. In this study, we concluded that pregnancy outcomes differed with disease severity, with the most increased risk for pre-eclampsia and preterm birth seen in pregnancies with antirheumatic treatment during pregnancy compared to non-PsA pregnancies.

In study IV, we wanted to investigate if disease activity influenced the risk of giving birth preterm. There are standardised ways to assess disease activity by a composite of clinical evaluation and biochemical testing. This assessment results in a score which can be used to evaluate disease activity in the clinical setting together with other factors. In a research setting like our study, the score alone can be used to characterise disease activity. All pregnancies in this study had PsA. We divided them into two groups based on whether they had any disease activity score indicating moderate or high active PsA disease or not. We assessed disease activity in the time period from one year before start of pregnancy until delivery. In pregnancies with a disease activity score indicating moderate or high active PsA disease any time during the study period, 13% had a preterm birth compared to 7.8% of those with scores indicating low active PsA disease. In conclusion, we found a numerical but not statistically significant difference between the proportions of preterm birth among PsA pregnancies with vs. without active disease during pregnancy.

To conclude: the studies included in this thesis indicate that pregnancies with JIA or PsA have less favourable outcomes compared to pregnancies without arthritis disease. However, most PsA and JIA pregnancies are also uneventful. The risk of preterm birth is influenced by disease severity and by whether the pregnancy is a first or subsequent pregnancy. It may also be influenced by disease activity.

ABSTRACT

The aim of this thesis was to add to the existing knowledge of how inflammatory arthritis disease affects pregnancy outcomes. In particular, the aim was to describe and study the effects of a diagnosis of juvenile idiopathic arthritis (JIA) or psoriatic arthritis (PsA) on pregnancy outcomes, to further study the effect of disease severity in PsA on pregnancy outcomes and lastly to study the association of disease activity and preterm birth in pregnancies with PsA. To address these aims we used information from Swedish population based registers such as the Medical Birth Register (MBR), the National Patient Register (NPR), the Prescribed Drug Register (PDR) and the nationwide clinical quality register, Swedish Rheumatology quality register (SRQ).

In study I-III, we used regression models to estimate odds ratios (ORs) with 95% confidence intervals.

In study I, we assessed pregnancy outcomes in a nationwide population based cohort of singleton pregnancies between 1992 and 2011. We identified 1807 pregnancies to women with a diagnosis of JIA and 1 949 202 comparator pregnancies to women without JIA. Due to the fact that JIA is a heterogenic condition, which may or may not persist into adulthood, we stratified the pregnancies with JIA into two groups: JIA paediatric only (n=1169), where the diagnosis was confined to childhood and/or adolescence, and JIA persisting into adulthood (n=638). In conclusion, we observed increased risks of preterm birth and caesarean delivery for both JIA groups compared to comparator pregnancies. In addition, we observed increased risks of pre-eclampsia and small for gestational age (SGA) birth in pregnancies with JIA persisting into adulthood.

In study II, we studied pregnancy outcomes in a cohort of 41 485 singleton pregnancies from 1997 to 2014 assembled by linkage of national registers. We identified 541 first and subsequent singleton pregnancies with PsA exposure and 40 944 pregnancies were identified as unexposed during the same time period. Pregnancies to women with PsA had increased risks (estimated with aORs) of preterm birth and caesarean delivery compared to unexposed pregnancies.

In study III, the focus was to assess how disease severity of PsA (by use of a proxy, i.e. antirheumatic treatment) affected pregnancy outcomes in comparison with non-PsA pregnancies. We defined the study period from 2007 to 2017 to be able to use information from the prescribed drug register. The main study cohort consisted of 921 PsA pregnancies and 9210 matched (on parity, maternal age and year of birth) non-PsA pregnancies. In the main analysis there were increased risks of preterm birth and caesarean delivery in PsA as compared to non-PSA pregnancies. We thereafter stratified the cohort of PsA pregnancies based on presence, timing and type of antirheumatic treatment. The risks of preterm birth and caesarean delivery differed among these groups, with the most increased risks among PsA pregnancies (vs. non-PsA) with antirheumatic treatment during pregnancy. Risk of preterm birth was influenced by parity and mainly increased in first pregnancies.

In study IV, we used information from SRQ and MBR to assemble a cohort of 211 pregnancies from 2007 to 2017. All identified pregnancies had a diagnosis of PsA assigned by the treating rheumatologist. We aimed to assess the association of disease activity, in the time period from one year before pregnancy until delivery, and preterm birth. Disease activity was assessed with registered values of DAS28CRP and values of health assessment questionnaire (HAQ). We dichotomised the exposure into moderate/high disease activity and low disease activity. The proportion of preterm birth was higher in pregnancies with any registered moderate/high disease activity in the year before and/or during pregnancy (vs. not). We found a numerical but not statistically significant difference between the proportions of preterm birth among PsA pregnancies with vs. without active disease during pregnancy.

LIST OF SCIENTIFIC PAPERS

I. **Juvenile onset arthritis and pregnancy outcome: a population-based cohort study**.
Remaeus K, Johansson K, Askling J, Stephansson O
Ann Rheum Dis. 2017;76(11):1809-14

II. **Maternal and infant pregnancy outcomes in women with psoriatic arthritis: a Swedish nationwide cohort study**.
Remaeus K, Stephansson O, Johansson K, Granath F, Hellgren K
BJOG. 2019;126(10):1213-22.

III. **Pregnancy outcomes in women with psoriatic arthritis with respect to presence and timing of antirheumatic treatment.**
Remaeus K, Johansson K, Granath F, Stephansson O, Hellgren K
Submitted to Arthritis & Rheumatolgy, revision due in June 2021.

IV. **Association of disease activity and preterm birth in pregnancies with psoriatic arthritis.**
Remaeus K, Johansson K, Granath F, Askling J, Stephansson O, Hellgren K
In manuscript.

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LIST OF ABBREVIATIONS

ACPA	Anti-citrullinated protein antibodies
ACR	American college of rheumatology
aOR	Adjusted odds ratio
AS	Ankylosing spondylitis
ATC	Anatomical therapeutic chemical
bDMARD	Biological disease-modifying antirheumatic drug
BMI	Body mass index
CASPAR	Classification of psoriatic arthritis
cDMARD	Conventional disease modifying antirheumatic drug
CI	Confidence interval
cJADAS-10	Clinical juvenile arthritis disease activity score 10 joint
CRP	C-reactive protein
CS	Corticosteroid
CV	Cardiovascular
CVD	Cardiovascular disease
DAS28	Disease activity score 28 joint count
DAS28CRP	Disease activity score 28 joint count-CRP
DMARD	Disease-modifying antirheumatic drug
ER	The Swedish educational register
ESR	Erythrocyte sedimentation rate
EULAR	European league against rheumatism
HAQ	Health assessment questionnaire
IBD	Inflammatory bowel disease
IBD-SpA	Inflammatory bowel disease related arthritis
ICD	International classification of diseases
IJD	Inflammatory joint disease
ILAR	International league of associations for rheumatology
JIA	Juvenile idiopathic arthritis
JRA	Juvenile rheumatoid arthritis
LBW	Low birth weight (≤ 2500 gram)

LGA	Large for gestational age
MBR	Medical Birth Register
NPR	National Patient Register
NSAID	Non-steroidal anti-inflammatory drug
OR	Odds ratio
PAS	Patient activity score
PDR	Prescribed Drug Register
PIN	Personal identity number
PPROM	Preterm pre-labour rupture of membranes
PR	The Swedish total population register
PsA	Psoriatic arthritis
Pso	Psoriasis
RA	Rheumatoid arthritis
ReA	Reactive arthritis
RF	Rheumatoid factor
SGA	Small for gestational age
SLE	Systemic lupus erythematosus
SpA	Spondyloarthritis
SRF	Svensk reumatologisk förening
SRQ	Swedish rheumatology quality register
TNF	Tumour necrosis factor
TNFi	Tumour necrosis factor inhibitor
uSpA	Undifferentiated spondyloarthritis
uSpA	Undifferentiated spondyloarthritis
VTE	Venous thromboembolism

1 INTRODUCTION

1.1 BACKGROUND AND CLINICAL CONTEXT

As an obstetrician, I meet and care for women having different types of medical conditions during their pregnancy and labour. In the beginning of my clinical career as an obstetrician in the late 1990s, I met many pregnant women with inflammatory rheumatoid conditions, most frequently severe systemic lupus erythematosus (SLE). I was taught that oestrogen and pregnancy may worsen some inflammatory conditions – such as SLE – whereas it could, conversely, induce amelioration for those with rheumatoid arthritis (RA). I remember that the women with RA were quite affected by their disease, not seldom in wheelchair and very often with visible destruction of joints. We often admitted them to in-patient care because of deterioration of symptoms or a need of surveillance. A few years after the new millennium, the patient panorama was totally different. Presumably, this was due to changes in the available treatment options, such as the introduction of biological disease-modifying anti rheumatic drugs (bDMARDs) including tumour necrosis factor inhibitors (TNFi).

These changes in the patient panorama, which we saw within the specialised obstetric care, sparked my curiosity about this group of pregnant women and this area of research.

With respect to pregnancy outcomes, RA is the most studied of the chronic inflammatory arthritis diseases. Due to a lack of specific information for other inflammatory arthritis diseases, results from studies on RA during pregnancy are often generalised to these conditions as well. In the clinical setting, disease specific information is needed to plan surveillance and care during pregnancy, as well as to inform and discuss expectations with the woman. Probably, some aspects of RA and pregnancy are indeed generalisable, but there may be differences that could be important to address.

Treatment options for various inflammatory conditions have increased and improved during recent years, why there is a need both to assess pregnancy outcomes in a contemporary patient population with adequate anti-rheumatic treatment and to further elucidate and disentangle what impact disease activity and/or severity may have on pregnancy outcomes.

2 LITERATURE REVIEW

2.1 INFLAMMATION AND PREGNANCY

Chronic inflammation, such as RA and inflammatory bowel disease (IBD), has been associated with an increased risk for adverse pregnancy outcomes (1-7) presumably linked to effects of inflammation, presence of autoantibodies, co-morbidities and medical treatment (7). Immunological, epidemiological and clinical evidence suggest that female sex hormones play an important role in the aetiology and pathophysiology of chronic immune and inflammatory diseases (7-9).

Outside pregnancy, the immune system is designed to protect the body from non-self-antigens, whereas self-antigens are expected to be tolerated. However, if a reaction against self-antigens occurs, it is generally considered to be an autoimmune reaction. Pregnancy is an exception, which induces changes in the immune system to tolerate the foetus, i.e. the immune system tolerates non-self tissues. The mechanisms underlying this tolerance have been the focus of research, but are not fully understood.

2.2 INFLAMMATORY ARTHRITIS AND PREGNANCY

In women with inflammatory arthritis, various adverse pregnancy outcomes have been reported for both the mother and the neonate. During pregnancy, pre-eclampsia is described, (5, 6, 10, 11) and in terms of mode of delivery, increased frequencies of caesarean deliveries are reported in women with inflammatory arthritis disease (10-15). Among foetal/neonatal complications, the most frequently described are preterm birth and neonates born small for gestational age (SGA) (2, 3, 6, 7, 14).

In 2016, Wallenius *et al.* published an informative study on reproductive trends in women with inflammatory joint disease (IJD); juvenile idiopathic arthritis (JIA), RA, psoriatic arthritis (PsA) and spondylarthritis (SpA), with respect to calendar time (14). The authors reminded the reader about the fact that several women with inflammatory arthritis were discouraged from pregnancy as late as the 1990s. Since then, the proportion of women with inflammatory disease who give birth has gradually increased, while adverse pregnancy outcomes have decreased (14). Also, diagnostic criteria have changed during the years, as well as available treatment and treatment strategies, both outside pregnancy (treat-to-target) and during pregnancy. In fact, TNFi are now accepted in guidelines for use in the first two trimesters for those with moderate or severe disease activity (6, 16-18).

In another study, Wallenius *et al.* (4) reported on adverse pregnancy outcomes in women with inflammatory arthritis related to birth-order, i.e. if the first birth was before or after diagnosis of inflammatory arthritis (4). This study describes increased frequency of pregnancy complications compared to the general population, but mainly in the first birth after diagnosis (14).

2.2.1 Rheumatoid arthritis

RA is a chronic inflammatory arthritis characterised by symmetric small joint polyarthritis, systemic inflammation and inflammation of the synovial membrane surrounding the joint.

The onset is usually at 40-70 years of age, and the disease is 2-3 times more common in women than in men. Furthermore, the onset of disease in women is common during times in life when sex hormones are fluctuating, such as the postpartum period and around the time of menopause (19). The prevalence of RA is approximately 0.5-1% in Western countries and the incidence among Swedish women is 56 per 100 000 (20, 21).

There is no diagnostic test for RA. Thus, the diagnosis is based on classification criteria and a physician's assessment. Since 2010, the updated ACR (American college of rheumatology)/EULAR (European league against rheumatism) scoring criteria for classification of RA are in use (22) (Table 1). The criteria focus on the early stages of the disease and distinguish between two different phenotypes based on serology, where presence of anti-citrullinated protein antibodies (ACPA) and/or rheumatoid factor (RF) is used (ACPA positive/negative or RF positive/negative). The criteria are intended for use in a target population with patients who: a) have at least one joint with definite clinical synovitis wherein b) the synovitis is not better explained by another disease. To be classified as RA, an overall score of ≥6 according to ACR/EULAR is required.

Table 1. ACR/EULAR scoring criteria for classification of RA

A. Joint involvement	**Score**
1 large joint	0
2-10 large joints	1
1-3 small joints	2
4-10 small joints (with or without involvement of large joints)	3
>10 joints (at least 1 small joint)	5
B. Serology (at least 1 test result is needed for classification)	**Score**
Negative RF and negative ACPA	0
Low-positive RF or low-positive ACPA	2
High-positive RF or high-positive ACPA	3
C. Acute-phase reactants (at least 1 test result is needed for classification)	**Score**
Normal C-reactive protein (CRP) and normal erythrocyte sedimentation rate (ESR)	0
Abnormal CRP or abnormal ESR	1
D. Duration of symptoms	**Score**
<6 weeks	0
≥6 weeks	1

2.2.1.1 Disease activity and severity

An activity index is of importance to determine disease activity, but the treating rheumatologist has to evaluate also clinical findings and bio-chemical variables to define disease activity since there is no single test to assess disease activity or level of inflammation. The activity index can be used to support the decision making.

The most widespread measure of disease activity is the 28-joint disease activity score (DAS28), which was originally developed to describe results in clinical trials (23). This index is a composite value consisting of swollen (0-28) and tender joint count (0-28), erythrocyte

sedimentation rate (ESR) and the patient's general health assessment on a visual analogue scale (0-100). Different versions of DAS28 are available. DAS28CRP (3) is calculated based on three variables: swollen and tender joint count and CRP. DAS28CRP (4) includes also patient global assessment (24).

DAS28 < 2.6 is defined as remission, DAS28<3.2 as low disease activity, DAS28 3.2-5.1 as moderate disease activity and DAS28>5.1 as high disease activity. When DAS28 is calculated based on CRP instead of ESR the same definitions are used (25, 26).

Health assessment questionnaire (HAQ) is an index of patient rated functional ability where a low value indicates good functional ability. With this index the restrictions of daily life activities due to the disease can be assessed. Stanford HAQ, full HAQ or HAQ- disability index (HAQ-DI) all refers to the original HAQ which was developed for use in patients with RA. The modified HAQ (mHAQ) is a shorter version of the full HAQ.

2.2.1.2 Pregnancy outcomes in RA pregnancies

RA is the most frequently studied condition among the chronic inflammatory arthritis during pregnancy. In 1938, Hench published a classic study about amelioration of RA related symptoms during pregnancy, and a similar pattern has been confirmed in later publications and by clinical experience throughout the years. (7) In more recent years, the PARA study (1, 27-31) (**p**regnancy-induced **a**melioration of **r**heumatoid **a**rthritis), consisting of a nationwide prospective cohort of about 245 RA women, (32) has contributed important insights on this subject in a more contemporary RA population. The percentage of patients who improved during pregnancy varied between 39-75%, depending on, among other things serological status (6, 33, 34). In one of the studies, the authors conclude that women with seronegative disease were more likely to improve during pregnancy as compared to those with seropositive disease (30). Increased disease activity postpartum was not dependent on serological status in this study population (30). In 2017, Ince-Askan *et al.* (31) published a study, also embedded in the PARA study, which reported that women with RA and a low disease activity score (in this study defined as DAS28CRP <3.2) were more likely to have a low disease activity score or to reach remission in the third trimester. This was irrespective of autoantibody status or use of prednisone (corticosteroid treatment). Also, women with higher disease activity who were not taking prednisone and lacked autoantibodies still had, as the authors phrased it, *"a fair chance of low disease activity in the last trimester"*. The opposite was noted for those with positive autoantibody status and a moderate or severe disease activity (DAS28CRP ≥3.2) in the first trimester; only 5.5% of these women were in remission in the third trimester (31). Notably, none of these women used bDMARDs and no other obstetrical outcomes regarding the mother and infant were studied.

Overall, studies have shown that neonates born to women with RA are more frequently born SGA and preterm, that this can to some extent be associated with disease activity (5, 6, 27), whereas the effect of corticosteroids on birth weight seems to be mediated by shorter gestational length at time of birth (27). Norgaard *et al.* observed an effect of autoantibody status when assessing pregnancy outcomes in a large Danish-Swedish population based cohort, comparing first time singleton pregnancies in mothers with RA to general population comparators (5). The adjusted odds ratio (aOR) for preterm birth, both moderately and very

preterm, were increased in the RF-positive group 1.65 (95%CI 1.23-2.23) and 2.04 (95%CI 1.18-3.53), respectively. No statistically significant associations were seen in the RF-negative group. The same pattern was seen when analysing the outcome of SGA births. There was also an increased prevalence of pre-eclampsia and caesarean deliveries when comparing women with RA to general population controls (5, 11).

The effect of corticosteroids on adverse outcomes is discussed in a systematic review by Bandoli *et al.* (35). The authors summarise that the use of corticosteroids during pregnancy may be associated with a modest increase of cleft lip (congenital malformation), but data are conflicting. Further, it is unknown to what extent maternal disease also affects this outcome. Bandoli *et al.* also state, with regard to systemic corticosteroid use during pregnancy, that there is little evidence of an independent risk increase of corticosteroids on preterm birth, low birth weight or pre-eclampsia.

Bharti *et al*. have performed a prospective cohort study of 440 women with RA to determine the effect of RA disease severity on pregnancy outcomes. Data collection period was from 2005-2013. This was a study on subjects enrolled in an ongoing project, inclusion criteria were birth of a live born singleton infant and that the subjects completed three telephone based measures of RA disease severity, prior to 20 weeks of gestation and after two and four weeks postpartum respectively. The measurements of RA disease severity included the health assessment questionnaire disability index (HAQ-DI), pain score and patients global scale. Data was self-reported and verified with medical records. The outcomes studied were preterm birth, SGA birth and caesarean delivery. The authors report an association between HAQ-DI, when used as a continuous variable and measured in early pregnancy, and preterm birth. No association was found for HAQ-DI and caesarean delivery. Overall, the women in the study population had a low median HAQ-DI of 0.25 indication mild disease (36).

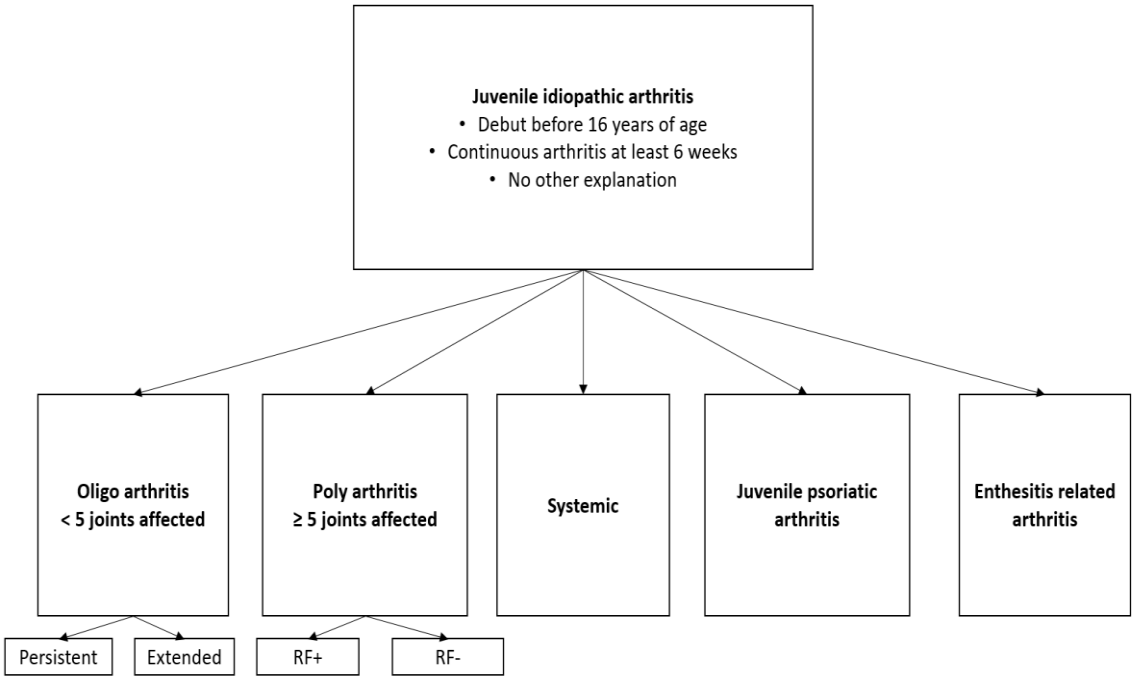
In 2019, Kishore *et al*. reported from a cross-sectional study where they compared pregnancy related admissions for women with RA and without where they used data from a nationwide inpatient database in the United States of America 2003-2011 (37). They identified 31 439 women with RA and 42 286 209 comparators without RA in the database. There were increased aOR of hypertensive diseases, premature rupture of membranes, antepartum haemorrhage, preterm birth, intrauterine growth restriction and caesarean delivery. The analyses were adjusted for age and co-morbidities. They did not have data on disease activity or antirheumatic treatment. This study is included in this literature review because it is a contemporary US based study with possibly a more diverse study population than in the smaller studies from Organization of Teratology Information Specialists (OTIS) Autoimmune Diseases in pregnancy Project (38, 39) which are described in the next paragraph about JIA.

2.2.2 Juvenile idiopathic arthritis

Juvenile idiopathic arthritis (JIA) encompasses a heterogeneous group of clinical phenotypes characterised by onset of arthritis before the age of 16 years. JIA constitutes the most common childhood rheumatic condition (40). JIA can mainly be divided into five subgroups depending on symptoms, number of joints affected by inflammation and serological markers (Figure 1). Since 1997, the International league of associations for rheumatology (ILAR) criteria are used for classification and an internationally accepted nomenclature for the

condition (JIA) is established. The incidence is estimated to 15/100 000 children and year in Sweden and to 11-14/100 000 children and year in the Nordic countries (41).

Figure 1. Subgroups of JIA according to the 1997 ILAR criteria.



Although the natural course of JIA is variable and may include remission, more than one third of all JIA patients have persisting disease into adulthood (42, 43). JIA may impact health in adulthood through several mechanisms: ongoing inflammatory activity and exposure to immune-modulatory therapies, systemic effects of past inflammatory activity such as impaired growth during adolescence and local effects such as joint destruction (44).

2.2.2.1 Pregnancy outcomes in JIA pregnancies

With respect to pregnancy outcomes in patients diagnosed with JIA, Ostensen *et al.* reported in 1991 on 76 pregnancies in women with JIA and suggested an increased risk of caesarean delivery (45). In 2013, Chen *et al.* reported on 78 births in women with JIA and found increased risks of caesarean delivery, pre-eclampsia and preterm birth (13). Ehrmann Feldman *et al*. reported 2016 on a large Canadian cohort study of first births to women with a history of JIA (n=1681). The study focused on neonatal outcomes and reported on higher proportions of prematurity, SGA and congenital malformations in the infants to women with a history of JIA as compared to infants born to mothers without JIA (46). The same authors published a study in 2017, using presumably the same study cohort, focusing on maternal postpartum outcomes. They describe an increased risk of venous thromboembolism (VTE) in mothers with JIA compared to unexposed mothers. The low number of events did not allow for full adjustment of covariates, but after adjustment for caesarean delivery the odds for VTE were increased 5-fold OR 5.29; 95% CI 1.84 -15.21. Similar results were found when adjustments for maternal age and pre-eclampsia, respectively, were performed in separate

analyses. The authors concluded: *"Mothers with JIA appear to be at higher risk for complications from anaesthesia, postpartum haemorrhage and thromboembolism*" (46).

Mohamed *et al*. studied the risk of preterm birth and restricted foetal growth in pregnant women with diagnosis of juvenile rheumatoid arthritis (JRA) compared to pregnant women without this diagnosis (47). It was a US based cross sectional study comprising women who delivered between 2011 and 2012. 1236 women had a diagnosis of JRA. Overall, the authors found an increased risk of preterm birth aOR 2.1, 95% CI 1.74- 2.42 in women with JRA compared to non-JRA. When stratified by race there were differences, aOR for preterm birth in Hispanic JRA women was 4.43 95% CI 2.97-6.62 compared to non-JRA Hispanic women and aOR for preterm birth in white women with JRA compared to non-JRA was 1.78, 95% CI 1.41-2.24. The proportion or odds of having a SGA birth did not differ between JRA and non-JRA women. Asians and Pacific Islanders did not have increased odds of preterm birth. The authors' state that they have defined the outcome preterm birth with ICD 9 code 644.0, with a reference to a webpage and year of access 2015. To my understanding this code refers to threatening premature labour (644.2 corresponds to early onset of delivery). Thus, the results from this study have to be interpreted with caution.

Ursin *et.al*. studied disease activity of JIA in 114 women (135 pregnancies) during and after pregnancy (48). Disease activity was assessed with DAS28CRP3 at seven time points before, during and after pregnancy when also self-reported physical function, pain and mental health was assessed. The study was register based and included pregnancies from 2006-2015. Women with at least one registered measurement from the first trimester to one year after delivery were included. The EULAR criteria was used to define categories of disease activity as in remission, low disease activity, moderate disease activity and high disease activity. Self-reported medical outcomes study short form (SF-36), a modified HAQ and information on medication were collected at each visit. The proportion of women using a DMARD (in this study synthetic, biological or both) decreased from 55% before pregnancy to 22% in pregnancy. 48 women discontinued bDMARD in the year prior to pregnancy. Of these, 23 did so more than three months before, 17 less than three months before and 8 at the time of confirmed pregnancy. Less than 5% of the women used bDMARD during pregnancy.

Almost 80% of the women in the study were in remission or had low disease activity throughout the study period. The authors conclude that disease activity was stable but was increased at the assessment six weeks postpartum. The patient reported MHAQ were highest in the third trimester corresponding to the lowest functionality. This was in line with the result from the physical functioning score of SF-26 which also was lowered in the third trimester compared to six weeks postpartum.

Apart from the study on exclusively women with RA mentioned in the previous RA-paragraph (36) a more recent study was published in 2019 on data from the same ongoing project: OTIS Autoimmune Disease in Pregnancy Project where pregnant women with both RA and JIA as well as comparison women were assessed regarding effects of maternal disease activity, medication use and pregnancy conditions effect on risk for preterm birth (39). 170 women with JIA, 657 women with RA and 564 comparison women without

autoimmune diseases were included. Live born infants from 2004 to 2017 were included in the analysis. Disease activity was documented at intake and at 32 weeks of gestation using patient reported assessments HAQ, pain score and patient global disease activity assessment which were used to calculate the patient activity scale (PAS) score where high disease activity was defined as PAS score >3.7 and low disease activity as ≤3.7. Active disease was associated with preterm birth in women with RA but not in JIA. After adjustment (including for disease activity) corticosteroid use in any trimester was significantly associated with preterm delivery in both women with RA and JIA. Neither DMARDs nor biologics were associated with increased risk for preterm birth. Further, pre-eclampsia, pregnancy induced hypertension and gestational diabetes were independently associated with a higher risk for preterm birth among women with RA but not in women with JIA. In women with JIA fever and NSAID medication were associated with preterm birth. The authors discuss if this may be indicators of active disease not captured by the disease activity measures used in the study.

In 2019 Förger *et al*. published another study from the OTIS Autoimmune Disease in Pregnancy Project with the aim to study patterns of TNFi continuation or discontinuation during pregnancy in association with changes in disease activity during pregnancy (38). 93 women with JIA were included together with 397 women with RA. Unfortunately, JIA was not analysed separately. In the study, 323 women (65.9%) received a TNFi during pregnancy and 122 discontinued before gestational week 20. 201 women continued their treatment and 116 of these women continued until term gestation. 85 women discontinued at a mean gestational age of 32 weeks. 167 women in the study did not receive any TNFi during pregnancy. At inclusion in the study, disease activity was low to minimal measured with PAS scores ≤3.7. In conclusion, the authors did not find a risk of worsening disease activity after discontinuation of TNFi before gestational week 20.

In 2020, a register based study from Taiwan was published including first singleton births in women with two diagnosis of JIA (defined by the authors) before 16 years of age and five matched, on maternal age and birth year, births to women without JIA (49). For infant outcomes the authors report increased aOR for low birth weight but comment that the absolute difference compared to the reference population was small. No difference with respect to outcomes preterm birth or SGA birth were seen. Regarding maternal outcomes there were no statistically significant differences. The authors discuss that sub types of JIA can differ between a Caucasian population, where pauciarticular arthritis is the most common subtype and an Asian population where enthesitis related arthritis is more common and that this may be a factor that contributes to the favourable outcomes seen in this study.

Recently, a study from Germany with data from two ongoing multicentre prospective observational cohorts the JIA registry Biologics in Paediatric Rheumatology (BiKeR) and its follow up register Juvenile arthritis Methotrexate/Biologics long term Observation (JuMBO) was published (50). They investigated the course and outcome of pregnancy in women with diagnosis of JIA (or recruited as female partners to a male JIA patient) and with long term or until pregnancy use of DMARDs during 2007-2018.

Patients were assessed every 6 months and both rheumatologist and patient reported outcomes were collected. Information about pregnancy was gathered once early in pregnancy and when the infant was 6 months of age. If complications were reported, written medical reports were requested from the attending physicians. The outcomes studied were disease activity measured with clinical arthritis DAS (cJADAS-10), live births and major congenital anomalies. The study included 119 women and 152 pregnancies. The largest JIA category was RF-negative polyarthritis (30%). The women were observed approximately eight years until conception and all were treated with DMARDs before, 92% bDMARDs. 67 pregnancies were exposed to DMARDs early in pregnancy and the median treatment length during pregnancy was six weeks. Disease activity was reported to be moderate before and during pregnancy and high afterwards when cJADAS-10 was used. DAS28CRP was reported to indicate a low mean disease activity before and after pregnancy and remission during pregnancy (<2.6), further patients with polyarthritis had lower disease activity than patients with enthesitis related arthritis or PsA. Pregnancy outcomes were assessed comparing DMARD exposed with DMARD unexposed and among live births only haemorrhage differed between the groups with increased frequency among unexposed compared to exposed.

In conclusion, studies regarding JIA and pregnancy outcomes are more common during the later years and include larger study populations which is promising. There are indications of increased proportions of preterm birth in pregnancies with JIA (13, 39, 51) and some studies report increased proportion of caesarean deliveries (13, 45). The comparison of studies is hampered by the different outcomes reported. More recent studies focus on disease activity and antirheumatic treatment which is very important but comparison of these studies are also complicated due to use of different measures of disease activity and different time points of assessment. Most studies use variations of DAS28, most suitable for RA. Given the heterogeneous presentation of JIA this assessment index may, for example be less suitable in the subgroup with enthesitis related arthritis and underestimate disease activity. Further, several of the studies are conducted in ongoing prospective pregnancy cohorts limiting assessment of disease activity to be based on telephone interviews as well as absence of a comparison group. More than one study is based on the US-Canadian OTIS Autoimmune Disease in Pregnancy Project where inclusion is voluntary which increases the risk of selection bias and may lead to less generalizable results.

2.2.3 Psoriatic arthritis

Psoriatic arthritis (PsA) is part of the spondylarthritis (SpA) group. This is a heterogeneous group of disorders with interrelated features more than distinct diseases, and includes ankylosing spondylitis (AS), psoriatic arthritis (PsA), reactive arthritis (ReA), inflammatory bowel disease related arthritis (IBD-SpA) and undifferentiated spondyloarthritis (uSpA). The various clinical forms include spinal (axial) features, peripheral arthritis, enthesopathy and extra-articular features such as uveitis, psoriasis and inflammatory bowel disease. Studies regarding the prevalence of SpA are few, reporting 0.2-1.2% for AS and about double for SpA (52, 53).

Psoriatic arthritis (PsA) is an inflammatory, seronegative (i.e. not associated with serum autoantibodies) arthritis associated with psoriasis (Pso), which is equally common among men and women. Pso is a chronic relapsing inflammatory skin disease, characterised by the presence of scaling lesions. Age of onset of PsA is typically between 30 and 55 years. PsA usually presents with variable patterns of joint and skin involvement and of degree of severity. Disease manifestations include a spectrum from mild mono/oligo arthritis to very severe, erosive and destructive polyarthritis. Several disease subsets have been defined according to joint involvement. For diagnosis of PsA, the CASPAR criteria (classification of psoriatic arthritis) have been used since 2006 (Table 2) (54).

Table 2. The CASPAR criteria for classification of PsA.

CASPAR criteria	
Requires the presence of inflammatory arthritis (in the joints, spine or enthesites) and ≥3p from the following	
At the time of examination	
• Current psoriasis or	2p
• Prior personal history of psoriasis or	1p
• Family history of psoriasis	1p
Nail psoriasis, including onycholysis, pitting and hyperkeratosis	1p
Absence of rheumatoid factor in blood tests	1p
Current or prior history of dactylitis	1p
Radiographic evidence of periarticular new bone formation (excluding osteophytes) on x-rays of the hand or foot	1p

According to the Swedish association of rheumatology (55), the prevalence of PsA in Sweden is 0.2% among adults. The corresponding figure is 2% for Pso, and among those, 15-30% are affected by any form of musculoskeletal engagement.

Both Pso and PsA are associated with co-morbidities including cardiovascular disease (CVD), obesity and the metabolic syndrome (56-59), with a corresponding significantly increased risk of cardiovascular events (58). The metabolic syndrome describes the presence of abdominal obesity, atherogenic dyslipidemia, hypertension, hyperglycaemia, insulin resistance, pro-inflammatory and a pro-thrombotic state (60). Studies have shown that the metabolic syndrome was equally associated with mild and severe psoriasis, and the cardiovascular co-morbidities were found to be equally prevalent in early and established PsA (61). Some evidence indicate that obesity may be a risk factor for developing PsA (62) based on the assumption that adiposity is associated with inflammatory cytokines known to be associated with Pso. Obesity is an independent risk factor for Pso (63). There are also studies stating that chronic inflammatory conditions, such as PsA, could be considered as independent risk factors for CVD and contribute to the large cardiovascular burden among these patients (64-67). EULAR recognises a higher risk of CVD in PsA patients, just as in RA and AS patients (68).

2.2.3.1 Pregnancy outcomes in PsA pregnancies

Studies on pregnancy outcomes in PsA are increasing in number (Table 3).

Table 3. Pregnancy outcomes in women with diagnosis of PsA.

Author, year	Diagnosis	N	Outcome	Conclusion/Result
Ostensen(69), 1988	PsA	12	Description of disease course	"PsA followed a pregnancy pattern resembling RA"
Mouyis et.al.(70) 2017	PsA	16	Disease activity and foetal outcomes	"PsA worsens during pregnancy and postpartum"
Polachek et.al.(71) 2017	PsA	42	Disease activity	"The outcome of pregnancy among patients with PsA is excellent"
Broms et.al,(72) 2018	PsA as subgroup	964	Adverse pregnancy outcomes	Increased risk of gestational hypertension, pre-eclampsia and elective caesarean delivery
Strouse et.al(73) 2018	PsA as a subgroup	161	Preterm birth, congenital anomalies, LBW, SGA	Increased odds of preterm birth,
Polachek,(74) 2019	PsA	151	Questionnaire based	Rate of live birth, vaginal delivery, gestational age and birth weight were similar compared to healthy controls. 58% reported favorable joint activity during pregnancy
Mörk,(75) 2019	SpA, PsA as a subgroup	130	Adverse pregnancy outcomes	Non-significant estimates of preterm birth, caesarean delivery aOR SGA 1.72 (0.98-3.02)
Ursin,(76) 2019	PsA	108	Disease activity DAS28CRP BASDAI	Disease activity was highest at 6 months postpartum. Women with TNFi had lower disease activity
Smith,(77) 2020	PsA	117	Adverse pregnancy outcomes accounting for disease activity	Increased risk of moderate preterm birth, oligohydramnios, caesarean delivery A high HAQ score at 32 gw associated to preterm birth

Three of the studies in this table are more descriptive (69-71) and two of them describe the outcome disease activity during pregnancy in opposite ways. Mouvis *et al*. concludes that PsA worsens during pregnancy and Polachek *et al*. concludes that the outcome among patients with PsA is excellent. This can be due to the limited number of pregnancies studied. However, there are somewhat conflicting results in the other studies as well. The largest cohort of PsA pregnancies is studied by Bröms *et al*. (72) including singleton pregnancies with births 2007-2012 from Sweden and Denmark. PsA was a subgroup in a larger cohort of Pso pregnancies. They report that women with PsA had increased risks of gestational hypertension aOR 1.60, 95% CI and preeclampsia aOR 1.49, 95% CI compared to pregnancies without Pso. Further, there was an increased risk of elective caesarean delivery. The proportion of preterm birth was 6% among PsA pregnancies compared to 5.4% in the non-Pso pregnancies and the PsA subgroup consisted of approximately 63% subsequent pregnancies and the comparison group 55%. The analyses were adjusted for parity among other confounders. However, the adjusted OR was 1.25, 95% CI 0.94-1.65.

Both Strouse *et al*. (73), and Smith *et al*. report increased risk of moderately preterm birth and in the latter study they were able to describe an association of high HAQ score at 32

gestational weeks (vs. not) and increased risk of outcome preterm birth (77). As well as in the large study by Bröms *et al*. there were increased risks of caesarean delivery and pre-eclampsia compared to a comparison group of pregnancies reported by Smith *et al*.

In a Danish cohort study of pregnancies with SpA 1997 to 2016 there was an increased risk of moderately as well as very preterm birth, elective caesarean delivery, emergency caesarean delivery as well as use of epidural analgesia (75). PsA pregnancies were analysed as a subgroup, the authors conclude that the prevalence of preterm birth and delivery by caesarean were increased for all subtypes of SpA compared to the reference group but least for PsA. No information about antirheumatic treatment or disease activity was presented in this study.

Ursin *et al*. (76) conducted a prospective study with the aim to study disease activity in women with peripheral PsA from pre conception to one year postpartum with the use of validated disease activity measures. The methodology is similar to what was described for assessing disease activity in JIA, a study by the same author (48). The study included women with a diagnosis of PsA 2006-2017 and all women defined as having PsA fulfilled the CASPAR criteria. The included women had data from at least one time point in pregnancy. The study cohort comprised 108 pregnancies. Mean number of visits per pregnancy was 4.4.

Disease activity was measured using the 3-variable Disease Activity Score in 28 joints (DAS28) using the CRP level (DAS28CRP3). Disease activity categories were defined according to EULAR criteria. To assess axial disease activity Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) was used. BASDAI is calculated from six patient reported items and give a final score 0-10 with 10 corresponding to maximal disease activity. Further, the assessed activity of psoriasis using the Psoriasis Area and Severity Index (PASI). Information about medication was collected at each visit.

Approximately 75% of the women were in remission or had low disease activity from time before pregnancy to one year postpartum even though use of DMARD decreased. The authors report variation in disease activity with amelioration in pregnancy and increased activity six months postpartum. The trend was the same for axial PsA and activity of psoriasis was low. The disease activity increased six months postpartum although TNFi was used of 40% the women.

2.2.3.2 Disease activity measures in PsA

PsA can often affect distal interphalangeal joints and the ankles, (78) and these joints are not counted in DAS28. Thus, using that index can underestimate disease activity in PsA. Even so, DAS28CRP has been validated and in use for assessing disease activity in PsA (79). In 2010 the Disease Activity Index for Psoriasis Arthritis (DAPSA) was launched (80). DAPSA is more extensive and is calculated from 66 joint count for swelling and 68 joint count for tenderness, patient global assessment, patient pain assessment and CRP. Neither DAS28CRP nor DAPSA assesses skin involvement, dactylitis, enthesites or axial involvement of the disease.

No specific pregnancy validated disease activity measure exists for PsA (81).

3 RESEARCH AIMS

3.1 AIM

The overall aim of this thesis is to study and describe the influence of inflammatory arthritis on pregnancy outcomes.

3.1.1 Specific aims

The specific aims are to study:

- The risk of adverse pregnancy outcomes associated with a history of juvenile JIA (Study 1)
- Whether women with PsA are at increased risk of adverse pregnancy outcomes (Study 2)
- Pregnancy outcomes in women with PsA with respect to presence, timing and type of anti-rheumatic treatment as a proxy for disease severity (Study 3)
- The association of disease activity and preterm birth in pregnancies with PsA (Study 4)

4 MATERIALS AND METHODS

4.1 SETTING

The studies in this thesis were all conducted in Sweden, where the opportunities to perform epidemiological research are eminent due to the structure of the health care system and the existence of the unique personal identity number. This number is assigned to each resident at birth or immigration and enables linkage between the nationwide registers which hold prospectively collected information on health and social factors for all inhabitants. (82) The main holders of the registers are the National Board of Health and Welfare and Statistics Sweden. An additional type of registers available in Sweden are the quality registers. These are established and developed by the medical profession for follow up of quality of care, procedures and given treatments. These registers are also utilised for research. Further, health care in Sweden is public and tax funded, making it accessible to all residents. In addition, all pregnant women are offered free antenatal and delivery care. More than 98% of pregnant women attend antenatal care and over 99% of all births take place in hospitals (83). As a result of the almost complete coverage of the national registers, study populations can be selected in an almost unbiased way.

4.2 DATA SOURCES USED

4.2.1 National registers

4.2.1.1 The National Patient Register

The National Patient Register (NPR) is kept by the National Board of Health and Welfare and consists of the Swedish Inpatient Register and the Swedish Outpatient Register. The NPR contains information on hospital discharges by county since 1964 and nationwide since 1987. Since 2001, nationwide data from specialist outpatient care (not primary care) are included in the register. The coverage is close to 100% for inpatient care and somewhat lower for outpatient care, mainly due to lower reporting from private and psychiatric care (84). Diagnoses and procedures are coded according to International Classification of Disease (ICD) versions 7 through 10. Information from the NPR was used in study I-III.

4.2.1.2 The Swedish Medical Birth Register

The Swedish Medical Birth register (MBR) is kept by the National Board of Health and Welfare and covers more than 98% of all births in Sweden from 1973 and onwards (85, 86). In the register, mothers and their infants are linked. From first attendance at antenatal care throughout pregnancy, delivery and the neonatal period, information is collected prospectively through structured forms filled out by midwives and physicians. The register includes information on identification and demographic data (for example country of birth), social factors such as cohabiting with the father, smoking habits and alcohol use, maternal medical history, information about pharmacological treatment and current BMI, and reproductive history (history of infertility, infertility treatments, number of previous pregnancies). During pregnancy, information is continuously added. Delivery characteristics such as time of birth, parity, maternal age, onset and mode of delivery, labour analgesia, foetal presentation and mode of birth as well as medical conditions and procedures are

recorded during delivery or at discharge from the delivery unit. ICD codes 8-10 are used for diagnoses. Information about the infant single or multiple birth, live or stillborn, gestational age, birth weight, length, sex, Apgar score, malformations and other diagnoses classified according to ICD during the neonatal period are also captured in the MBR. Information from the MBR was used in study I-IV.

4.2.1.3 The Prescribed Drug Register

The Prescribed Drug Register (PDR) contains information on all dispensed prescriptions of drugs (amount and dates) classified according to the Anatomical Therapeutic Chemical (ATC) classification system from Swedish pharmacies since July 2005 (87). The register does not include data on drugs administrated or used in hospitals. Information from the PDR was used in study III.

4.2.1.4 The Swedish Educational Register

The Swedish Educational Register (ER) is held by Statistics Sweden and contains information about the highest level of completed education of all Swedish citizens 16-74 years of age. Information about foreign-born citizens' educational level is gathered yearly via surveys. Information from the ER was used in study I-III.

4.2.1.5 The Swedish Total Population Register

The Swedish Total Population Register (PR) is maintained by Statistics Sweden and holds census data since 1968. The register contains data on birth, death, name change, marital status, family relationships and migration within Sweden as well as to and from other countries (88). Information from the PR was used in study II-IV.

4.2.2 Quality Registers

4.2.2.1 The Swedish Rheumatology Quality Register

The Swedish Rheumatology Quality Register (SRQ) was started in 1995 and is maintained by the Swedish Society of Rheumatology. It was originally a clinical quality register of patients with RA. With time, it has developed to include also patients with many other rheumatic diagnoses, including PsA, with the aim to improve care and treatment. Data is collected longitudinally by both care givers (rheumatologists and nurses) and patients. The register includes information on diagnosis and disease debut, dates of visits, anti-rheumatic treatment and disease activity measures. Since 1999, the SRQ includes the Swedish Biologics Register, ARTIS (Antirheumatic Treatment in Sweden) a register for patients with any rheumatic disease who start biological treatment. ARTIS was started in collaboration with the Swedish Medical Products Agency with the primary aim to evaluate the safety of biologic drugs. The coverage in the register of patients with RA, PsA, AS and SpA diagnoses on biologic therapy is high, 95% for RA diagnosis and 86% for AS, PsA and SpA (89). Information from SRQ was used in study III and IV.

4.3 STUDY POPULATIONS AND STUDY DESIGNS

All studies included in this thesis use pregnancies and births as study subjects, i.e. the individual women are not studied.

Table 4. Overview of study characteristics.

	Study I	**Study II**	**Study III**	**Study IV**
Design	Register based cohort	Register based cohort	Matched register based cohort -matching variables in the main cohort maternal age, year of birth and parity	Register based cohort
Years of delivery	1992-2011	1997-2014	2007-2017	2007-2017
Data sources	MBR, NPR, ER	MBR, NPR, PR, ER	MBR, NPR, PR, ER, PDR, SRQ	SRQ, MBR
Number of study subjects	1 951 009	41 485	10 131	211
Exposure variable/-s	Juvenile onset arthritis	PsA	PsA	DAS28CRP HAQ
Outcome measures	-Pre- eclampsia -Stillbirth -Preterm birth (overall, very and moderately) -Spontaneous or induced preterm birth -Mode of onset of labour -Mode of delivery -Early (0-27days) neonatal death -Apgar score <7 at 5 minutes -SGA	-Pre-eclampsia -Gestational diabetes -Stillbirth -Preterm birth (overall, very and moderately) -Spontaneous or medically indicated preterm birth -PPROM -Mode of onset of labour -Mode of delivery -Apgar score <7 at 5 minutes -Early (0-27 days) neonatal death -SGA -LGA	Pre-eclampsia -Gestational diabetes -Gestational hypertension -Preterm birth (overall, very and moderately) -Spontaneous or medically indicated preterm birth -Emergency or elective caesarean delivery -SGA -LGA	-Preterm birth
Co variates	-BMI -Calendar year of birth -Country of birth -Educational level -Maternal age -Parity -Smoking habits	-BMI -Calendar year of birth -Country of birth -Educational level -Maternal age -Parity -Smoking habits	-BMI -Calendar year of birth -Country of birth -Educational level -Maternal age -Parity -Smoking habits	-

4.3.1 Study I

4.3.1.1 Study population in study I

We identified births from 1992 until 2011 in the MBR and merged this with information from the NPR and the ER. After exclusion of multiple births (n=59 259), births with missing or invalid personal identity number (n=2434) and births to women with a diagnosis of systemic inflammatory and connective tissue diseases (identified via ICD codes versions 8-10) to avoid misclassification of the exposure (n=9407), the final study cohort consisted of 1 951 009 births.

4.3.1.2 Exposure in study I

The exposure juvenile onset arthritis was defined according to ICD codes (Table 5) with the requirement of at least one listing diagnosis of JIA in inpatient or outpatient care from paediatric, paediatric surgery, internal medicine or rheumatology departments before 18 years of age. Because the definition of the diagnosis JIA requires debut or disease onset before 16 years of age, and this does not match the Swedish cut-off age between paediatric and adult care which is 18 years of age, we included both those with JIA diagnosis and those with diagnoses of PsA, AS, RA and inflammatory spondyloarthritis before 18 years of age. Since JIA is a heterogenic condition that may or may not persist into adulthood, we created two subgroups of births within the exposed JIA births. The first subgroup was considered to have JIA confined to childhood and adolescence and included births to women with onset of JIA before 18 years of age or a diagnosis of any of the corresponding adult arthritis diagnoses listed in Table 5 before 18 years of age, but without any visit or hospitalisation with any of these diagnoses after the age of 18 until delivery. This subgroup was described as "JIA paediatric only" (n=1169). The second subgroup included births to women with a diagnosis of JIA who also had at least one visit or hospitalisation for a diagnosis of chronic inflammatory arthritis after the age of 18 years but before delivery. This group was described as "JIA persisting into adulthood" (n=638).

Table 5. ICD codes used for exposure variable in Study I

Diagnosis	ICD-10-SE	ICD-9-SE	ICD-8-SE
Juvenile onset arthritis	M08-9	714D	712,00
	M05 M06.0 M06.2-3 M06.8-9 M12.3	714A 714B 714C 714W 719D	712,10 712,20 712,38 712,39
	M45	7120A	712,40 726,99
	M46.0-1 M46.8-9	720C 720W 720X	713,12 713,19 726,99
	L40.5 M07.0-1 M07.3	696A 713D	696,00

4.3.1.3 Outcomes in Study I

Outcomes pre-eclampsia and eclampsia were analysed among all births and were identified via ICD 9 codes 642E-G and ICD 10 codes O14- O15. Gestational age at delivery was used to categorise pre-eclampsia as early onset (diagnosis and birth before gestational week 34+0) or late onset (diagnosis and birth ≥34+0). Also, the outcome stillbirth was analysed among all births and defined as intrauterine death after gestational week 28 from 1992 to 30 June 2008 and after gestational week 22+0 from 1 July 2008. The other outcomes were analysed among live births. We assessed preterm birth, defined as birth before 37+0 gestational weeks and categorised them into very preterm birth (birth < 32+0 gestational weeks) and moderately preterm birth (32+0 to 36+6 gestational weeks). Further, we categorised the preterm births by type of onset; spontaneous or medically indicated (induced labour). Onset of labour was categorised into spontaneous or induced and mode of delivery into vaginal birth, assisted vaginal birth and birth by caesarean section. The latter were categorised as emergency or elective (planned). For foetal outcomes we assessed neonatal death (death before 28 days), Apgar score <7 at 5 minutes and SGA which was defined as a birth weight of more than two SD below the sex-specific mean for gestational age (90).

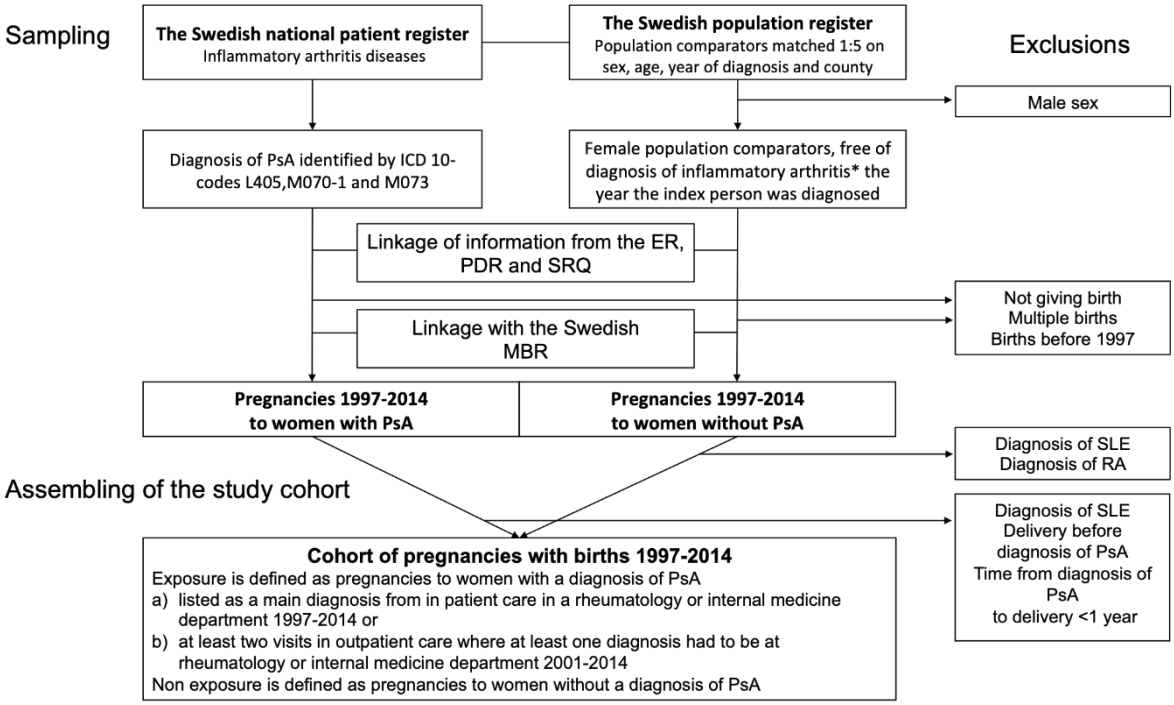
4.3.2 Study II

4.3.2.1 Study population in study II

We created a study cohort of 41 485 first and subsequent singleton pregnancies with births occurring 1997 to 2014.

These births were identified from an existing linkage where individuals with chronic inflammatory diagnoses were identified from NPR and matched to five comparator subjects based on age at index person's diagnosis, calendar year, sex and county. This original linkage was also, for example, enriched with information from the ER, MBR and SRQ.

F**igure 2**. Flow chart with schematic information of sampling process and assembling of the study cohort in study II.



PsA= psoriatic arthritis, Inflammatory arthritis*= juvenile idiopathic arthritis, ankylosing spondylitis, rheumatoid arthritis, undifferentiated spondyloarthritis, psoriatic arthritis, SLE= systemic lupus erythematosus

4.3.2.2 Definitions and descriptions of variables used in study II

Table 6. Definitions and descriptions of variables used in study II or III.

Variables used	Register	ICD 10 code	Description for the purpose of this study
Exposure variable			
Psoriatic arthritis (PsA)	NPR, inpatient and outpatient care	L405 M070 M071 M073	Requirement of a main diagnosis from inpatient care in the department of rheumatology or internal medicine or requirement of two separate visits in outpatient care with at least one in the department of rheumatology or internal medicine. Diagnosis one year before date of conception to be considered as exposure.
Co-morbidities and other arthritis diseases			
Juvenile idiopathic arthritis (JIA)	NPR	M08 M09	One listing at department of rheumatology or internal medicine. Diagnosis of JIA was allowed before first diagnosis of PsA but not after. In that case the birth was considered to be non-PsA.
Ankylosing spondylitis (AS)	NPR	M45	One listing at department of rheumatology or internal medicine.
Inflammatory bowel disease (IBD)	NPR	K50-K51	Any diagnosis
Antiphospholipid syndrome (APS)	NPR	D686 A-C	Any diagnosis
Diabetes mellitus type 1	NPR	E10	Diagnosis one year before conception to be considered as an existing pre pregnancy condition.
Chronic hypertension	NPR	I10-I15	Diagnosis one year before conception to be considered as an existing pre pregnancy condition.
Treatment for infertility	MBR		Checkbox in the register.

Diagnoses for exclusion			
Systemic lupus erythematosus (SLE)	NPR	M320 M321 M328 M329	One visit in at the department of rheumatology or internal medicine. If a diagnosis of SLE was present the pregnancy was excluded.
Rheumatoid arthritis (RA)	NPR	M05M 060M0 62M06 3M068 M069 M123	One listing at the department of rheumatology or internal medicine. If a diagnosis of RA occurred before diagnosis of PsA, the birth was considered to be **non**-PsA
Outcome variables			
Pre-eclampsia	MBR	O14- O15	The clinical definition of preeclampsia during the study period was two blood pressure measurements of ≥140/90 with at least 4h apart combined with proteinuria (≥0.3 grams per 24 h or one or more on a urine dipstick on at least two subsequent occasions)
Early onset pre-eclampsia	MBR	O14- O15	Onset of pre-eclampsia and delivery < 34+0 gestational weeks (gw)
Late onset pre-eclampsia	MBR	O14- O15	Onset of pre-eclampsia and delivery ≥ 34+0 gw
Gestational diabetes	NPR	O244	New onset diabetes during pregnancy
Preterm birth	MBR		Birth before gw 37+0
Moderately preterm birth	MBR		Births between gw 32+0-36+6
Very preterm birth	MBR		Births between gw 22+0-31+6
Spontaneous onset of preterm birth	MBR		If gestational age at delivery was preterm and the onset of labour was spontaneous or preterm pre-labour rupture of membranes (PPROM) the onset was considered spontaneous.
Medically indicated onset of preterm birth	MBR		If the gestational age at delivery was preterm and the onset of labour wasn't spontaneous we considered it medically indicated.
Preterm pre-labour rupture of membranes (PPROM)	MBR	O42	In conjunction with preterm delivery (gestational age at birth)
Induction of labour	MBR	O61	Checkbox in the register and ICD code
Caesarean delivery (all)	MBR	O82	Both elective and emergency caesarean deliveries
Elective caesarean delivery	MBR		Planned caesarean delivery before start of labour
Emergency caesarean delivery	MBR		Not planned caesarean delivery
Assisted vaginal delivery	MBR		Delivery/birth by vacuum extraction or forceps
Small for gestational age (SGA)	MBR		Birthweight below 2 standard deviations (SD) of sex - specific mean weight per gestational age
Large for gestational age (LGA)	MBR		Birthweight above 2 standard deviations (SD) of sex - specific mean weight per gestational age
5 min Apgar score <7	MBR		
Neonatal death	MBR		Infant death 0-27 days after birth
Stillbirth	MBR		Non-live birth ≥ 22+0 gw since 1st of July 2008, before that non-live birth ≥ 28+0 gw

4.3.2.3 Exposure in study II

Exposure in this study was PsA, defined with ICD-10 codes L405, M070-1 and M073, as a) a main diagnosis from inpatient care at a rheumatology or internal medicine department 1997-2014 or b) at least two visits in outpatient care with the diagnosis of PsA at a rheumatology or internal medicine department 2001-2014. First singleton pregnancies after 1997, and subsequent pregnancies, with this exposure were identified in the existing linkage. If time from diagnosis of PsA and delivery was less than one year, the pregnancy was excluded. Also, pregnancies with a diagnosis of SLE or RA before birth (Figure 2) were excluded.

Unexposed pregnancies and births were identified as all of the matched population comparator persons' pregnancies regardless if they were sampled originally as a comparator for another inflammatory arthritis diagnosis than PsA. In theory, all of the population comparator births had the possibility to change group and be exposed during the study period, if the sampled comparator individual was diagnosed with PsA.

4.3.2.4 Outcomes in study II

Outcomes pre-eclampsia and eclampsia were identified via ICD-10 codes O14- O15 and analysed among all births. Gestational age at delivery was used to categorise pre-eclampsia as early onset (diagnosis and birth before gestational week 34+0) or late onset (diagnosis and birth ≥34+0). The outcome stillbirth was defined as intrauterine death after gestational week 28 from 1992 to 30 June 2008 and after gestational week 22+0 from 1 July 2008. Gestational diabetes was identified via ICD-10 code O24.4 as new onset diabetes during pregnancy. The other outcomes were analysed among live births. We assessed preterm birth, defined as birth before 37+0 gestational weeks and categorised them into very preterm birth (birth <32+0 gestational weeks) and moderately preterm birth (32+0 to 36+6 gestational weeks). Further, we assessed preterm pre labour rupture of membranes (PPROM) and we categorised the preterm births by type of onset; spontaneous or medically indicated. Onset of labour was categorised into spontaneous, induced or by elective caesarean delivery. Mode of delivery was categorised into vaginal birth, assisted vaginal birth and birth by caesarean delivery. The latter were categorised as emergency or elective (planned). For foetal outcomes we assessed Apgar score <7 at 5 minutes, SGA birth, large for gestational age (LGA) birth and neonatal death (death before 28 days).

4.3.3 Study III

4.3.3.1 Study population in study III

We assembled a study cohort of 10 131 singleton pregnancies with births in the study period 1 April 2007 to 31 December 2017. The start of the study period was selected to enable inclusion of data from the PDR.

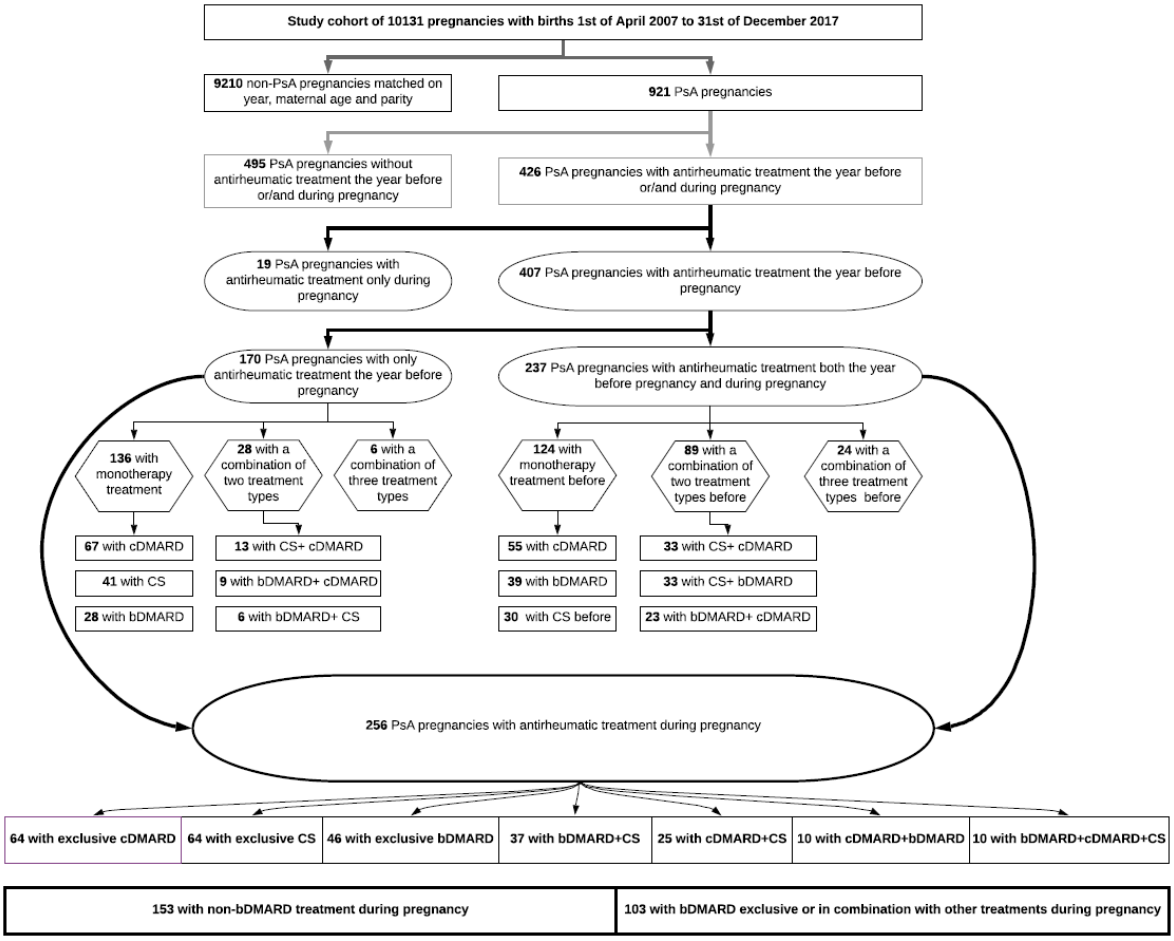
The study cohort was sampled in the same way as described in Figure 2/study II but with an updated linkage including information on births until 31 December 2017. In this study cohort, we identified 921 exposed pregnancies and matched them to 10 unexposed pregnancies based on year of birth, maternal age and parity.

4.3.3.2 Exposure(s) in study III

The main exposure was diagnosis of PsA, identified with an ICD-10 code of L405, M070-1 or M073 in NPR, with at least two listings/visits with this diagnosis, at least one being at the department of rheumatology or internal medicine. Furthermore, the diagnosis had to have been present at least one year before start of pregnancy.

We used presence, timing and type of antirheumatic treatment as a proxy for PsA disease severity and assessed this in several subgroups where we stratified the exposure to diagnosis with or without different types of antirheumatic treatment in different pre-specified time frames of each pregnancy.

Figure 3. Flow chart showing different stratified analysis groups in study III with pregnancies based on presence, timing and type of antirheumatic treatment.



The PDR holds information on all filled prescriptions at Swedish pharmacies since July 2005, including date of dispensing and the ATC code indicating the drugs. For this study, we defined antirheumatic treatment as oral corticosteroids, conventional (c) or biological (b) disease modifying antirheumatic drugs (DMARDs). ATC codes were used to identify antirheumatic treatment (Table 7). One filled prescription in the PDR in the pre-specified time frames (from one year before the start of pregnancy to delivery) was considered as treatment. As the PDR does not include data on drugs administrated in day-care units in hospitals, we retrieved information on infusion of infliximab from the Swedish Rheumatology Quality Register (SRQ).

Table 7. ATC codes used to identify antirheumatic treatment in study III.

ATC codes used to identify anti-rheumatic treatment	
Oral corticosteroids	H02AB01,-04,-06,-07
Conventional synthetic disease modifying drug (cDMARD)	A07EC01,-05, L04AA13, L04AD01, L04AX01, L01BB01, L01BA01, L04AX03, M01CB01, M01CB3, P01BA01, P01BA02, L04AAD02, L04AA06 and M01CC01
Biological DMARDs (bDMARD)	L04AB01, L04AB04, L04AB05, L04AB06, L01XC02, L04AA24, L04AC03 and L04AC07

To arrive at the different restricted subgroups of pregnancies based on presence and timing of antirheumatic treatment, we first divided the 921 PsA pregnancies into 495 pregnancies without any treatment from one year before pregnancy until delivery and 426 PsA pregnancies with any antirheumatic treatment in the same time frame (Figure 3). The latter pregnancies included 19 pregnancies with no treatment before, but treatment only during pregnancy and 407 pregnancies with treatment in the year before pregnancy irrespectively of treatment during pregnancy. These 407 pregnancies were further stratified into 170 pregnancies with treatment only in the year before pregnancy (no treatment during pregnancy) and 237 pregnancies with treatment both in the year before and during pregnancy. Finally, the 19 pregnancies with treatment only during pregnancy were added to the 237 pregnancies with treatment both before and during pregnancy resulting in the last stratified group with 256 pregnancies with antirheumatic treatment during pregnancy.

4.3.3.3 Outcomes in study III

We used ICD-10 codes to identify pre-pregnancy co-morbidities, such as hypertension and diabetes mellitus type, as well as outcomes including pre-eclampsia (including eclampsia O14-O15), gestational diabetes (O244) and gestational hypertension (O13). Gestational age was estimated by ultrasonography or, if ultrasonography was unavailable, by the recorded date of the first day of the last menstrual period.

Preterm birth was defined as birth before 37 completed weeks of gestation (gw) and further sub-categorised into moderately preterm birth (32+0 to 36+6 gw) or very preterm birth (22+0 to 31+6 gw). We sub-categorised preterm birth by onset (spontaneous or medically indicated). Further caesarean deliveries were sub-categorised into emergency or elective. For outcomes in the neonates we assessed SGA and LGA.

4.3.4 Study IV

4.3.4.1 Study population in study IV

The study cohort consisted of 211 singleton pregnancies resulting in a live birth from 1 January 2007 to 31 December 2017 with a maternal diagnosis of psoriatic arthritis (n=189) or juvenile psoriatic arthritis (n=22).

We defined maternal PsA as all women in the SRQ registered with the diagnosis PsA (or juvenile psoriatic arthritis) by their treating rheumatologist.

The study period of interest for each individual pregnancy was from one year before the start of pregnancy until the time point of delivery. This time period was divided into three month strata starting one year before date of conception and ending at the time point of delivery. The last stratum could thus be of different length for different pregnancies, because a pregnancy with a term birth can last from 259 to 294 days, i.e. a difference of more than a month.

4.3.4.2 Exposure in study IV

The exposure was measures of disease activity, DAS28CRP and HAQ, retrieved from SRQ. A DAS28CRP of ≥3.2, corresponding to moderate to high disease activity, and/or a HAQ score of >0.5 was considered as active PsA disease.

Pregnancies identified in SRQ but without registrations of disease activity during the time period of interest in this study were kept in the cohort for comparison, even though they were considered unexposed.

We identified 110 pregnancies, corresponding to 52% of the study population, with at least one registered DAS28CRP value during the study period. Among these 110 pregnancies, 46 had a registered DAS28CRP ≥3.2 at any time (i.e. from one year before start of pregnancy until birth) and 64 pregnancies had a registered DAS28CRP <3.2 (and no registered DAS28CRP values ≥3.2 during the study period) 101 of the 211 pregnancies in the study population did not have a registered value on DAS28CRP during the study period.

Regarding HAQ, we identified 118 pregnancies with a registered HAQ score during the study period. Of these, 62 pregnancies had registered a score of >0.5, and 56 pregnancies had registered values ≤0.5. 93 of the 211 pregnancies did not have any registered HAQ score during the study period.

4.3.4.3 Outcome in study IV

The outcome of interest in this study was proportion of preterm birth in relation to registered high vs. low disease activity. Preterm birth was defined as a birth before 37 completed weeks of gestation. Gestational length was retrieved from the MBR.

4.4 STATISTICAL ANALYSES

4.4.1 Statistical methods

4.4.1.1 Chi-squared test, Fisher's exact test and Wilcoxon two sample test

A chi-square (χ^2) test is used to determine whether there is a statistically significant difference between the expected and observed frequencies in one or more categories in a contingency table where the observations are classified in two mutually exclusive classes.

Fisher's exact test is a statistical significance test used in the analysis of contingency tables and is equivalent to the chi-square test but can be used even if the expected cell count is below five. The p-value from the test is computed as if the margins of the table are fixed.

Wilcoxon two sample test, also named Wilcoxon-Mann-Whitney is a non-parametric test that can be used when the variables not are normally distributed.

4.4.1.2 Logistic regression

Logistic regression analysis is used to determine the statistical relationship or association between one or more independent (predictor or explanatory) variable(s) and a dependent (outcome) variable. In a binary logistic regression, the dependent variable is dichotomous in two mutually exclusive levels (yes/no). The independent variable can be dichotomous, categorical or continuous. To model a linear relationship, the dependent variable is transformed by the logit function. The results of a logistic regression are presented as an odds ratio (OR) for which confidence intervals may be estimated. With a rare outcome (as a rule of thumb when the outcome is below 10%) the OR approximates a risk ratio (RR), the so called "rare disease assumption". For more common outcomes, the OR overstates the relative risk.

4.4.1.3 Other regression models

Even though binary outcomes are often analysed with a logistic regression model to obtain ORs, there may be situations, for example with a common outcome, where it would be desirable to estimate a RR instead. Typically, in such cases, a log binomial regression model is proposed. The difference from a logistic regression model is the *link* between the independent variable and the probability of the outcome. For logistic regression, the *logit link* is used, whereas for log binomial it is the *log link* which is used. Apart from this, both models assume that the error terms have a binomial distribution. The log binomial model may give narrower confidence intervals than what is true. Furthermore, this model may have difficulties to converge (91). If so, a Poisson regression model with a robust error variance can be used. The Poisson regression model assumes a Poisson distribution for the outcome, i.e. the occurrence of an outcome is equally likely at any point in time, and the probability of an outcome occurring is proportional to the length of time you wait. Initially, the model was recommended for studies of rare diseases where patients may be followed for different lengths of time. However, the model can be used with a time-at-risk value specified as 1 for each subject. The recommendation of using robust variance estimates originates from the observation that if you do not, the model estimates too wide confidence intervals (92, 93).

4.4.1.4 Generalised estimating equation

The generalised estimating equation (GEE) is used to account for correlation between dependent observations in a study population. GEE estimates population averaged model parameters and their standard errors.

4.4.1.5 Multiple imputation

Missing data is common, as there will be values missing in almost every dataset or source. When using regression models, the analyses will be performed on complete cases, i.e. the model only uses those observations for which information is complete. This can reduce statistical power and also result in biased estimates. Data can be missing for different reasons; 1) missing completely at random (MCAR) 2) missing at random (MAR) and 3) missing not at random (MNAR). Different types of missing data require different treatment. Multiple imputation, one method to handle missing data, generally assumes that the data are at least MAR, but this procedure can also be used if data is MCAR. The purpose when addressing missing data is to reproduce the variance/covariance matrix which would have been observed if no information was missing from the data. Multiple imputation is a general approach to missing data which aims to allow for the uncertainty about the missing data by creating several different plausible imputed data sets and combining results obtained from each of them. There are several steps in the procedure. First, the imputed values are sampled from the predicted distribution based on the observed data. The imputed values replace the missing values in several copies of the data set. Second, a statistical model is fitted to the imputed sets; in these, the estimated associations will differ according to the variation in the imputation of the missing values. They are averaged to give overall estimated associations.

4.4.1.6 Interaction analysis

An interaction analysis is conducted to estimate the possible effect modification of an interaction variable. A significant interaction indicates that the effect of one independent variable on the outcome variable varies at different values of the other independent variable. Interaction may be tested by adding the interaction term to a regression model.

All analyses included in this thesis were performed using SAS software version 9.4.

4.4.2 Statistical methods and sensitivity analyses used in study I-IV

4.4.2.1 Study I

In study I, we assessed differences between births in mothers with JIA and the reference population with regards to categorical data, by a χ^2 test where $p<0.05$ was considered statistically significant.

Unconditional logistic regression analyses were performed to estimate crude and adjusted ORs (aORs) with associated 95% CIs for outcome variables. The GEE method was used in the model to account for the clustering due to the inclusion of multiple births from the same mother. In the adjusted analyses, we adjusted for possible confounders that is maternal age at delivery, parity, BMI, smoking habits, educational level, the mother's country of birth and calendar year of birth.

We used a formal interaction test in the model to estimate possible effect modification between the exposure status*diabetes on the outcome pre-eclampsia. Several sensitivity analyses were performed. In the first sensitivity analysis, we redefined exposure to increase validity and decrease risk of misclassification of exposure by requirement of two listings or visits with diagnoses of JIA or corresponding arthritis diagnoses before the age of 18. We performed separate analyses for JIA paediatric and persisting. In the second sensitivity analysis, we restricted the analysis to births occurring 2002-2011 to assess if there existed possible calendar time dependent changes of care, both in obstetrics and rheumatology, which affected the estimates. To further assess possible effects of calendar time and changes in care procedures, we restricted a third analysis to births identified during the years 1987-2011 when ICD-9 and ICD-10 codes were in use. In a fourth sensitivity analysis, we performed an analysis restricted to births with JIA paediatric from 2003 and onwards with a requirement of at least two years from last diagnosis until delivery. This was to ensure that we did not misclassify a birth as JIA paediatric when it should be defined as JIA persisting into adulthood. Because the out-patient part of NPR is available since 2001 and more women may have listings in out-patient care than in in-patient care, we assumed that this could influence our analysis.

4.4.2.2 Study II

In study II, we assessed differences in maternal characteristics between exposed and unexposed births by a χ^2 test or Fischer's exact test. Furthermore, we estimated crude and adjusted ORs with estimated 95% CI for the outcome variables using a generalised linear regression model and a GEE method, with the mother's identification as a cluster and assuming an exchangeable correlation structure. This model provided the best (smallest) QIC (quasi-likelihood under the independence model criterion) value when we selected statistical model (negative binomial, logistic regression model, Poisson regression model).

In the adjusted analysis, we used several covariates: country of birth categorised into Nordic and non-Nordic, educational level categorised as ≤12 years or >12 years, smoking status as self-reported information from first antenatal visit categorised into smoker or non-smoker, parity (except in the sensitivity analysis of parity) as primiparous or parous, maternal age categorised into 13-24, 25-29, 30-34 and >35 years of age, calendar year of birth categorised in 1997-2002, 2003-2008 and 2009-2014. Further, BMI calculated from measured weight and self-reported height at the first antenatal visit and categorised as underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25-29.9 kg/m^2) and obese (≥ 30 kg/m^2).

Because BMI is associated with both exposure and outcome, it could be treated as a confounder. However, there are reports that state that weight gain can be an effect of an inflammatory condition (94) or other factors (95), so we estimated ORs both with and without adjustment for BMI.

We performed both a complete case analysis and an analysis were variables with missing information were imputed using multiple imputation. The missing information were imputed in the following order: education, country of birth, preterm birth, low Apgar score (Apgar score <7 at 5 minutes), small or large for gestational age, smoking status and BMI category. Education was imputed using the variables PsA status, maternal age, parity, gestational

diabetes, mode of delivery, pre-eclampsia and neonatal death as predictors. In the following imputation steps, all the variables previously imputed were additionally included as predictors. Fifty imputed data sets were created and analysed by logistic regression applying the GEE method when estimating parameters and co-variance matrices. These were analysed by the procedure MIANALYZE in SAS software version 9.4.

We performed several sensitivity analyses: a) an analysis restricted to first pregnancies, b) an analysis restricted to subsequent pregnancies, c) analyses restricted to pregnancies without ankylosing spondylitis, inflammatory bowel disease or rheumatoid arthritis before pregnancy and d) complete case analysis for comparison.

4.4.2.3 Study III

Baseline pregnancy characteristics were presented and calculated as counts and percentages. Odds ratios were estimated using a generalized model with logit link and assumption of binominal distribution as crude and adjusted odds ratios (ORs), with associated 95% confidence intervals. The analyses were performed on individual pregnancies. Because one woman could contribute more than one pregnancy, we used the GEE method with mother's identification as a cluster assuming an exchangeable correlation structure.

No risk estimates were calculated for outcomes with fewer than five events. Statistical interaction was assessed by inclusion of the interaction term exposure status (PsA)*parity. As the interaction term was significant for the outcome preterm birth, the analyses regarding this outcome were stratified on parity.

All analyses were performed on complete data.

Adjustments in the main analysis were made for the highest attained level of education, smoking status, BMI and country of birth. In the stratified analyses, the matching was broken and adjustment for maternal age, year of birth and parity was made in addition.

4.4.2.4 Study IV

Maternal characteristics were presented with counts and frequencies for categorical variables and medians with corresponding inter-quartile ranges for continuous variables. We assessed differences with Wilcoxon two-sample test in the continuous variables (values of DAS28CRP and HAQ), and used Fisher's exact test or χ^2 test for categorical variables. A p-value <0.05 was considered as indicating statistical significance.

4.5 ETHICAL CONSIDERATIONS

The main ethical concern in register-based research is to maintain the personal integrity of the study subjects. Generally, when research involves human subjects, informed consent should be obtained from each study subject. In practice, it is not possible to collect informed consent from the usually large number of subjects included in register-based studies. This is also the case for the studies included in this thesis. According to the Swedish Ethical Review Act (2003:460), research without informed consent from study subjects can be conducted if the results could be beneficial for the study subject or for others with the same condition (Ethical Review Act, 21 §). The results of the studies included in this thesis will hopefully contribute

to increased knowledge about inflammatory arthritis and pregnancy outcomes, which can be implemented in clinical praxis and be beneficial in the future.

Furthermore, the anonymity of the study subjects must be ensured and the handling of personal information is regulated in the Swedish Personal Data Act (PUL [*SFS 1998:204]*). The personal identification number of the study subjects included in register-based studies (also for the studies in this thesis) has been replaced with a random number by the National Board of Health and Welfare.

5 RESULTS

5.1 STUDY I

5.1.1 Summary of main findings in study I

Juvenile onset arthritis is associated with adverse pregnancy outcomes compared to population controls. We have identified increased risks of preeclampsia and preterm birth, as well as increased proportions of labour induction and caesarean deliveries.

5.1.2 Main results in study I

We identified 1807 singleton births in women with a diagnosis of JIA before delivery and 1 949 202 population comparator births during the study period 1992-2011. The births were stratified as JIA paediatric only n=1169 and JIA persisting into adulthood n=638. Regarding maternal characteristics, there were differences between the exposed and unexposed births. The women with JIA were younger, more often had births later in the study period, were to a larger extent born in a Nordic country, had underweight, lower educational level and were more frequently smokers. In the analysis of pregnancy outcomes, there were generally stronger associations with increased aORs in the JIA persisting into adulthood group compared to population comparator births. Regardless of how the exposure was defined or how the time frame in which the birth was assessed, we did not find any increased risk of stillbirth, early neonatal death or Apgar score <5 in any of the analyses. In the analyses we adjusted for maternal age, parity, BMI, calendar year of birth, smoking habits, highest attained educational level and the mother's country of birth.

5.1.3 Analyses in the subgroup JIA paediatric only

When we analysed births in women with JIA paediatric only compared with population comparator births there were increased risks of preterm birth, moderately preterm birth and medically indicated preterm birth aOR 1.32, 95%CI 1.00-1.76, aOR 1.43, 95%CI 1.07-1.91 and aOR 1.74, 95%CI 1.35-2.67 respectively. Further, induction of labour was more common aOR 1.45, 95%CI 1.18-1.77 as well as birth by caesarean delivery aOR 1.42, 95%CI 1.66-1.73. Both risk of emergency and elective caesarean delivery was increased with aOR 1.37, 95%CI 1.08-1.74 and aOR 1.39, 95%CI 1.08-1.78 respectively. There were no statistically significant increased risks of pre-eclampsia, spontaneous onset preterm birth, assisted vaginal delivery, Apgar score <7 at 5 minutes, SGA, LGA, stillbirth or early neonatal death (death 0-27 days) compared to population comparator births.

When we required two visits or hospitalisations with ICD code to fulfil the exposure criteria of JIA, the number of identified pregnancies were reduced, as expected, n=507. Generally, the point estimates were lower and did not remain statistically significant. In this analysis only the aOR for caesarean delivery was significantly increased compared to population comparator births.

In the third sensitivity analysis where only ICD-9 and ICD-10 codes were used for definition of the exposure n=379, the pattern of increased risks was almost the same as in the main analysis. The exception was that medically indicated preterm birth aOR 1.67 95% CI 0.72-

3.88 did not reach statistical significance, and neither did elective caesarean delivery. The point estimates for preterm birth and moderately preterm birth were somewhat more pronounced than in the main analysis, aOR 1.67, 95% CI 1.06-2.63 and aOR 1.89, 95%CI 1.20-2.89 respectively.

Furthermore, an analysis of the main exposure was made with a restriction to births 2002-2011 in order to better capture visits before pregnancy in the outpatient register n=636. This birth cohort was thought to reflect a different patient population than an inpatient defined exposure, as well as a more contemporary cohort of births. In this analysis, we noted the same pattern of increased risks as in the main analysis.

5.1.4 Analyses in the subgroup JIA persisting into adulthood

Births to women with JIA persisting into adulthood had increased risk of pre-eclampsia aOR 2.31, 95% CI 1.61-3.32. When the outcome pre-eclampsia was stratified into early onset, defined as diagnosis and birth before 34+0 gestational weeks, or late onset defined as diagnosis and birth ≥34+0 gestational weeks, both ORs were significantly increased compared to population comparator births. The aOR for early onset pre-eclampsia was 6.28 with 95% CI 2.86-13.81 and was based on a small number (n=9) of pregnancies with the outcome in the exposed group. Increased risk of late onset pre-eclampsia was also observed aOR 1.96, 95% CI 1.31-2.91.

When we required two visits or hospitalisations with correct diagnostic code to fulfil the exposure criteria of JIA, the point estimates were almost the same as in the main subgroup analysis (Table 8).

In the second sensitivity analysis where we restricted the exposure to those with a diagnosis from ICD-9 and ICD-10, the results resembled those of the main analysis with the exception of the outcome very preterm birth which was not statistically significant (Table 8).

In a third sensitivity analysis of births to women with JIA persisting into adulthood with restriction to births (n=492) 2002-2011, the pattern was the same as in the main analysis (Table 8).

Table 8. Adjusted* ORs with 95% CI in the subgroup JIA persisting into adulthood compared to population comparator births in main analysis and sensitivity analyses.

	Main subgroup exposure n=638	**Restricted to 2 diagnoses <18 years of age n=452**	**Restricted to exposure defined by ICD-9/10 n=436**	**Restricted to births 2002-2011 n=492**
	aOR (95% CI)	**aOR (95% CI)**	**aOR (95% CI)**	**aOR (95% CI)**
All births				
Pre-eclampsia	2.31 (1.61-3.32)	2.39 (1.58-3.62)	2.24 (1.45-3.45)	2.38 (1.60-3.54)
Early onset pre-eclampsia**	6.28 (2.86-13.81)	6.52 (2.55-16.69)	4.50 (1.67-12.14)	4.07 (1.51-10.99)
Late onset pre-eclampsia***	1.96 (1.31-2.91)	2.04 (1.30-3.18)	2.03 (1.27-3.25)	2.23 (1.31-2.91)
Live births				
Preterm delivery (<37+0 gw)	2.40 (1.81-3.18)	2.38 (1.70-3.32)	2.37 (1.69-3.34)	2.21 (1.59-3.06)
Moderately pre-term delivery	2.27 (1.68-3.08)	2.07 (1.42-3.00)	2.36 (1.64-3.40)	2.10 (1.47-2.99)
Very preterm delivery	3.14 (1.58-6.24)	4.42 (2.22-8.81)	2.31 (0.96-5.61)	2.85 (1.35-6.03)
Preterm delivery, medically indicated	4.12 (2.76-6.15)	5.07 (3.28-7.84)	4.10 (2.52-6.68)	3.94 (2.48-6.25)
Preterm delivery, spontaneous	1.63 (1.11-2.39)	1.28 (0.78-2.11)	1.65 (1.04-2.61)	1.48 (0.95-2.31)
Induction of labour	1.37 (1.07-1.75)	1.51 (1.13-2.00)	1.42 (1.06-1.90)	1.36 (1.03-1.79)
Assisted vaginal delivery	0.97 (0.68-1.38)	0.89 (0.58-1.38)	1.00 (0.67-1.48)	0.99 (0.68-1.45)
Caesarean delivery	2.47 (1.99-3.08)	2.63 (2.03-3.39)	2.08 (1.60-2.71)	2.17 (1.70-2.77)
Elective caesarean delivery	3.01 (2.32-3.90)	3.28 (2.45-4.39)	2.19 (1.55-3.09)	2.46 (1.83-3.31)
Emergency caesarean delivery	1.57 (1.19-2.08)	1.60 (1.15-2.23)	1.73 (1.24-2.41)	1.57 (1.15-2.13)
SGA	1.84 (1.19-2.85)	2.02 (1.23-3.32)	1.60 (0.96-2.69)	1.70 (1.02-2.85)

*Adjusted for maternal age at delivery, parity, BMI, calendar year of birth, smoking habits, educational level and the mother's country of birth.

5.1.5 Analyses of proportions of pre-eclampsia by adverse outcomes

Since several of the obstetrical outcomes can be interrelated and depend on each other, we estimated the proportion of pre-eclampsia in selected adverse outcomes stratified by subgroup of JIA compared to population comparator births (Table 9). In births with JIA paediatric only, there were no apparent differences in the proportion of pre-eclampsia in exposed vs. unexposed births regarding the adverse outcomes. In births with JIA persisting into adulthood there were generally higher percentages with pre-eclampsia in the exposed vs. unexposed births. In medically indicated preterm births, 45.5% had a diagnosis of pre-eclampsia compared to 36.6% of the unexposed births. Furthermore, 32% of the SGA births were affected by pre-eclampsia in the exposed group, compared to 14% in the unexposed. Among the adverse outcomes caesarean delivery and elective caesarean delivery, the differences were smaller; 11.3% vs. 7.2% and 13.3% vs. 7.9% respectively.

Table 9. Proportions of pre-eclampsia by adverse outcomes in births with JIA paediatric only compared to population comparator births and JIA persisting into adulthood compared with population comparator births.

	JIA paediatric only		JIA persisting into adulthood	
Pre-eclampsia	**No n (%)**	**Yes n (%)**	**No n (%)**	**Yes n (%)**
	Preterm birth (n=96 492)			
No n (%)	84 500 (87.6)	61 (88.4)	84 507 (87.6)	54 (77.1)
Yes n (%)	11 923 (12.4)	8 (11.6)	11 915 (12.4)	16 (22.9)
	Medically indicated preterm birth (n=29 072)			
No n (%)	18 415 (63.4)	18 (69.2)	18 415 (63.4)	18 (54.6)
Yes n (%)	10 631 (36.6)	8 (30.8)	10 624 (36.6)	15 (45.5)
	Caesarean delivery (n=280 182)			
No n (%)	259 909 (92.8)	181 (91.4)	259 925 (92.8)	165 (88.7)
Yes n (%)	20 075 (7.2)	17 (8.6)	20 071 (7.2)	21 (11.3)
	Elective Caesarean delivery (n=134 427)			
No n (%)	123 752 (92.1)	87 (92.6)	123 741(92.1)	98 (86.7)
Yes n (%)	10 581 (7.9)	7 (7.5)	10 573 (7.9)	15 (13.3)
	SGA birth (n=50 713)			
No n (%)	43 413 (85.7)	23 (88.5)	43 417 (85.7)	19 (67.9)
Yes n (%)	7274 (14.4)	3 (11.5)	7268 (14.3)	9 (32.1)

The reference groups (population comparators) include all births without JIA paediatric only and JIA persisting into adulthood respectively.

5.2 STUDY II

5.2.1 Summary of main findings in study II

Pregnancies with exposure of PsA are associated with increased risks of preterm birth and caesarean delivery. Risk of preterm birth differed by parity, where subsequent pregnancies did not have an increased risk compared to non-PsA pregnancies.

5.2.2 Main results in study II

We identified 541 singleton pregnancies in 330 women with a diagnosis of PsA, and 40 944 pregnancies in 25 594 women without a diagnosis of PsA during the study period 1997-2014. In comparison to non-PsA pregnancies, the PsA pregnancies had higher frequencies of co-morbidities such as IBD, affecting 2.8% of the PsA pregnancies compared to 0.9% of the non-PsA pregnancies, AS 2.0% among PsA pregnancies vs. < 0.01% in non-PsA pregnancies and RA 5.9% vs. 0.02%. Pre-pregnancy hypertension was more common in PsA pregnancies vs. non-PsA pregnancies: 0.4% vs. 0.1%, thus the absolute number was low (n=2) among the PsA pregnancies. This was likewise true for pre-pregnancy type 1 diabetes mellitus, (n=5) among PsA pregnancies corresponding to 0.9% compared to 0.4% among non-PsA

pregnancies. Furthermore, the women with PsA were more obese, more often smokers and more frequently born in the Nordic countries.

Overall, there was an increased risk of preterm birth among PsA pregnancies vs. non-PsA pregnancies, aOR 1.63; 95% CI 1.17-2.28, both with spontaneous onset, aOR 1.51; 95% CI 1.01-2.24 and medically indicated, aOR 1.85; 95% CI 1.04-3.27. The risk of moderately preterm birth was increased whereas very preterm birth was not. PsA pregnancies likewise had an increased risk of caesarean delivery, aOR 1.52; 95% CI 1.21-1.91 and risks of both emergency and elective caesareans were increased aOR 1.43; 95% CI 1.08-1.88 and aOR 1.47; 95% CI 1.10-1.97 respectively. There were no increased risks of pre-eclampsia, gestational diabetes, PPROM, SGA or LGA. Neither stillbirth, Apgar score <7 at 5 minutes or neonatal death.

Full adjustment, for year of birth, maternal age, parity, smoking, the mother's country of birth and educational level, including also BMI did affect the point estimates to some extent regarding pre-eclampsia aOR 1.21; 95% CI 0.78–1.88 in the fully adjusted model compared with aOR 1.33; 95% CI 0.86–2.05, gestational diabetes aOR 1.26; 95% CI 0.54–2.94 in the fully adjusted model compared with aOR 1.53; 95% CI 0.66–3.56 and LGA aOR 1.18; 95% CI 0.70–1.97 in the fully adjusted model compared with aOR 1.30; 95% CI 0.78–2.17. Full adjustment with BMI did not affect the estimates for preterm birth or caesarean delivery.

5.2.3 Effect of parity

When we analysed first and subsequent pregnancies separately, the risk of preterm birth was exclusively increased in first but not in subsequent pregnancies (Table 10). Conversely, risk of emergency caesarean delivery was significantly increased in subsequent, but not in first PsA pregnancies vs. subsequent non-PsA pregnancies.

Table 10. Comparison of selected outcomes stratified in first and subsequent pregnancies.

	First pregnancies			**Subsequent pregnancies**		
	PsA n=**330**	**Non-PsA** n=**25 594**	**Adjusted OR***	**PsA** n=**211**	**Non-PsA** n=**15 315**	**Adjusted OR***
All births	**n (%)**	**n (%)**	**aOR* (95% CI)**	**n (%)**	**n (%)**	**aOR* (95% CI)**
Gestational diabetes	5 (1.5)	239 (0.9)	1.53 (0.62-3.77)	1 (0.5)	119 (0.8)	
Live births	n=**328**	n=**25 497**		n=**209**	n=**15 183**	
Preterm birth <37 gw	35 (10.7)	1461 (5.7)	1.90 (1.33-2.72)	6 (2.8)	533 (3.5)	0.83 (0.36-1.90)
Spontaneous preterm birth	25 (7.6)	1068 (4.2)	1.85 (1.23-2.80)	3 (1.4)	405 (2.6)	
Medically indicated preterm birth	10 (3.0)	393 (1.5)	1.89 (1.00-3.59)	3 (1.4)	128 (0.8)	
Very preterm birth < 32 gw	5 (1.5)	191 (0.7)	1.94 (0.79-4.76)	1 (0.5)	66 (0.4)	
Moderately preterm birth 32-37 gw	30 (9.3)	1270 (5.0)	1.89 (1.29-2.76)	5 (2.4)	467 (3.1)	0.77 (0.31-1.90)
Assisted vaginal delivery**	54 (18.4)	3405 (14.4)	1.34 (1.00-1.81)	2 (1.1)	437 (3.2)	
Caesarean delivery	85 (25.9)	5107 (20.0)	1.37 (1.06-1.76)	51 (24.2)	2345 (15.3)	1.83 (1.30-2.58)
Elective caesarean delivery	34 (10.4)	1840 (7.2)	1.49 (1.04-2.14)	28 (13.3)	1553 (10.1)	1.47 (1.10-1.97)
Emergency caesarean delivery**	51 (17.3)	3267(13.8)	1.25 (0.92-1.71)	23 (12.6)	792 (5.8)	2.21 (1.40-3.48)

*Adjusted for year of birth, maternal age, parity, smoking, the mother's country of birth, educational level and BMI
**Estimates without elective caesarean deliveries in the denominator

5.2.4 Assessment of effect of co-morbidities and RA

Because co-morbidities and conditions associated with a diagnosis of PsA were more common, as expected, in the group of PsA pregnancies, we performed a sensitivity analysis in which pregnancies with a diagnosis of IBD, AS or RA before delivery were excluded. There were 483 PsA pregnancies in this analysis, compared to 40 499 non-PsA pregnancies. The proportion of preterm birth among PsA pregnancies was 7.4% compared to 7.6% in the main analysis and aOR of preterm birth compared to non-PsA pregnancies was 1.59; 95% CI 1.09-2.32 which was substantially the same as in the main analysis. Spontaneous preterm birth occurred in 4.8% of the PsA pregnancies in the restricted group compared to 5.2% in the main analysis. The ORs for spontaneous and medically indicated preterm birth were not statistically significantly increased in the restricted analyses, aOR 1.40; 95% CI 0.89-2.19 and 1.88; 95% CI 0.94-3.75 respectively. The aOR for caesarean delivery in the restricted analysis was 1.41; 95%CI 1.08-1.84, that is largely the same as in the main analysis (aOR 1.52; 95% CI 1.21-1.91). In the restricted analysis, the aOR for elective caesarean delivery was 1.28, 95% CI 0.90-1.82 vs. 1.47, 95% CI 1.10-1.97 in the main analysis indicating that the increased risk seen in the main analysis were due to factors carried by pregnancies with either co-morbidities or RA. The aORs for emergency caesarean were comparable 1.44; 95% CI 1.05-1.98 in the restricted analysis and 1.43; 95% CI 1.08-1.88 in the main analysis.

5.3 STUDY III

5.3.1 Summary of main findings in study III

PsA pregnancies are associated with increased risk of preterm birth compared to non-PsA pregnancies as well as caesarean deliveries. The risks differ by presence, timing and type of antirheumatic treatment as well as with parity. Most increased risk for preterm birth were noted in pregnancies with bDMARD treatment during pregnancy; aOR 4.49 95% CI 2.60-7.79.

5.3.2 Main results study in study III

In the matched main analysis of 921 PsA pregnancies compared to 9210 non-PsA pregnancies, the characteristics of women with PsA differed from non-PsA women regarding country of birth, where PsA women more often were born in the Nordic countries. Furthermore, PsA women were more obese (19.9% vs. 12.6%), more likely to be smokers (9.2% vs. 5.3%) and had a higher level of education; 50.1% vs. 43.3% had more than 12 years of education. Even though the numbers were low, it was also more common in women with PsA to have pre-pregnancy hypertension (1.4%) or diabetes mellitus (1.3%) compared to non-PsA women (0.8% and 0.5%, respectively).

In the main analysis of 921 PsA pregnancies vs. 9210 non-PsA pregnancies, we observed increased risk of preterm birth aOR of 1.69, 95%CI 1.27-2.24. There were also statistically significant increased risks for spontaneous onset and medically indicated preterm birth as well as for moderately preterm birth, but not for very preterm birth. Also, there was an elevated risk of caesarean delivery, both elective aOR 1.77, 95%CI 1.43-2.20 and emergency aOR 1.42 95%CI 1.10-1.84. There were no differences in risk of pre-eclampsia, gestational

diabetes or hypertension, SGA or LGA in PsA pregnancies compared to non-PsA pregnancies.

Generally, throughout the stratified analyses based on different aspects of antirheumatic treatment, we observed increased risks of preterm birth and caesarean delivery in all analyses. Risk of pre-eclampsia was increased only in the analysis of PsA with bDMARD treatment during pregnancy compared to non-PsA pregnancies aOR 2.88, 95% CI 1.35-6.17. We did not observe an increased risk of gestational diabetes nor gestational hypertension in any analysis. Further, there was no indication in proportions or when assessing adjusted ORs (including adjustment for BMI, country of birth, parity and smoking apart from the matching factors) of increased risk of SGA birth. Regarding LGA the results differed, with an increased risk in PsA pregnancies with any treatment before and/or during pregnancy compared to non-PsA pregnancies 6.6% vs. 3.9% and aOR 1.59, 95% CI 1.02-2.48. Among PsA pregnancies with treatment only before pregnancy 7.7% had a LGA birth vs. 3.9% in non-PsA pregnancies, aOR 1.76, 95% CI 0.95-3.24. Among PsA pregnancies with treatment during pregnancy 5.9% had a LGA birth aOR 1.48, 95% CI 0.82-2.68 compared to non-PsA pregnancies. There were 7.8% LGA births among bDMARD treated pregnancies aOR 2.21, 95% CI 0.97-5.05 compared with non-PsA pregnancies.

5.3.3 Analyses of preterm birth stratified on presence, timing and type of antirheumatic treatment

Compared with non-PsA pregnancies where 4.6% had a preterm birth, there were higher proportions of preterm birth in all stratified subgroups of PsA. Stratified on presence of treatment, no vs. any treatment; 7.1% of PsA pregnancies without treatment one year before or during pregnancy (n=495) delivered preterm as compared to 8.9% of the PsA pregnancies with any treatment during the time frame. When exposure was stratified on timing of treatment, 7.7% of pregnancies with treatment only before pregnancy (n=170) delivered preterm compared to 9.8% of those with treatment during pregnancy (n=256). And finally when pregnancies with treatment during pregnancy were further stratified into type of treatment, non-bDMARD and bDMARD treatment, 4.6% of the pregnancies with non-bDMARDs treatment had a preterm birth in contrast to 17.5% of those with bDMARDs.

In Table 11, the different aspects of preterm birth – overall estimate, stratified regarding onset and stratified by gestational age – are presented with stratified exposure with respect to presence of treatment. In Table 12 this is presented with respect to timing of treatment and, finally, in Table 13 presented with respect to type of treatment during pregnancy.

5.3.3.1 Preterm birth with respect to presence of antirheumatic treatment

There was increased risk of medically indicated preterm birth among PsA pregnancies without any treatment one year before pregnancy until birth, aOR 2.23, 95%CI 1.29-3.86. However, no other significant increased risk of preterm birth was noted compared to non-PsA pregnancies. Among the PsA pregnancies with treatment any time before and/or during pregnancy, there were increased risks of preterm birth, spontaneous preterm birth and moderately preterm birth (Table 11).

Table 11. Percentages and adjusted ORs of different components of preterm birth in analyses with exposure of PsA stratified on presence of antirheumatic treatment compared with non-PsA pregnancies. Preterm birth is defined as birth before 37+0 gestational weeks (gw), moderately preterm birth=32+0-36+6 gw and very preterm birth= <32+0 gw.

	Non-PsA pregnancies n=**9172**	**PsA pregnancies without treatment before and/or during pregnancy** n=**493**	**Adjusted* OR**	**PsA pregnancies with treatment before and/or during pregnancy** n=**425**	**Adjusted* OR**
	n (%)	**n (%)**	**aOR* (95% CI)**	**n (%)**	**aOR* (95% CI)**
Preterm birth	417 (4.6)	35 (7.1)	1.43 (0.96-2.12)	38 (8.9)	**1.98 (1.37-2.86)**
Spontaneous onset	277 (3.0)	18 (3.7)	0.98 (0.58-1.69)	25 (5.9)	**1.98 (1.27-3.09)**
Medically indicated	140 (1.5)	17 (3.5)	**2.23 (1.29-3.86)**	13 (3.1)	1.86 (0.98-3.50)
Very preterm	61 (0.7)	5 (1.0)	1.82 (0.66-5.00)	2 (0.5)	-
Moderately preterm	356 (3.9)	30 (6.2)	1.38 (0.90-2.11)	36 (8.5)	**2.15 (1.47-3.14)**

*Adjustments were made for maternal age, country of birth, year of birth, parity, educational level, smoking status and BMI

5.3.3.2 Preterm birth with respect to timing of antirheumatic treatment

Among PsA pregnancies with antirheumatic treatment only before pregnancy, there were no statistically significant increased risks of preterm birth. On the contrary, among PsA pregnancies with treatment during pregnancy there were increased risks of preterm birth, spontaneous preterm birth and moderately preterm birth (Table 12).

Table 12. Percentages and adjusted ORs of different components of preterm birth in analyses with exposure of PsA stratified on timing of antirheumatic treatment compared with non-PsA pregnancies. Preterm birth is defined as birth before 37+0 gestational weeks (gw), moderately preterm birth= 32+0-36+6 gw and very preterm birth= <32+0 gw.

	Non-PsA pregnancies n=9172	**PsA-pregnancies with treatment only before pregnancy n=169**	**Adjusted*OR**	**PsA pregnancies with treatment during pregnancy n=256**	**Adjusted* OR**
	n (%)	**n (%)**	**aOR* (95% CI)**	**n (%)**	**aOR* (95% CI)**
Preterm birth	417 (4.6)	13 (7.7)	1.44 (0.75-2.77)	25 (9.8)	**2.30 (1.49-3.56)**
Spontaneous preterm	277 (3.0)	8 (4.7)	1.25 (0.55-2.86)	17 (6.6)	**2.43 (1.45-4.06)**
Medically indicated	140 (1.5)	5 (3.0)	1.76 (0.63-4.91)	8 (3.1)	1.90 (0.88-4.13)
Very preterm	61 (0.7)	2 (1.2)	-	0 (0.0)	-
Moderately preterm	356 (3.9)	11 (6.6)	1.44 (0.72-2.86)	25 (9.8)	**2.58 (1.66-4.00)**

*Adjustments were made for maternal age, country of birth, year of birth, parity, educational level, smoking status and BMI

5.3.3.3 Preterm birth with respect to type of antirheumatic treatment during pregnancy

PsA pregnancies with antirheumatic treatment during pregnancy were stratified on those treated with non-bDMARDs (corticosteroids and/or cDMARDs) and bDMARDs (exclusively or in combination with corticosteroids and/or cDMARDs). 153 pregnancies were identified with non-bDMARD treatment and 103 with bDMARD treatment. Among the 153 pregnancies with non-bDMARD treatment there was no increased risk of preterm birth. On the contrary, among the 103 pregnancies with the bDMARD treatment the risks of preterm birth were increased. The aOR for spontaneous birth among PsA pregnancies with bDMARD treatment compared to non-PsA pregnancies was 4.49, 95% CI 2.60-7.79. For spontaneous onset preterm birth aOR 4.73, 95% CI 2.53-8.87, for medically indicated preterm birth the aOR was 3.29, 95% CI 1.28-8.46 and aOR for moderately preterm birth was increased as well, 5.06, 95% CI 2.91-8.79 (Table 13).

Table 13. Percentages and adjusted ORs of different components of preterm birth in analyses with exposure of PsA stratified on type of antirheumatic treatment compared with non-PsA pregnancies. Preterm birth is defined as birth before 37+0 gestational weeks (gw), moderately preterm birth= 32+0-36+6 gw and very preterm birth= <32+0 gw.

	Non-PsA pregnancies n=9172	**PsA pregnancies with non-bDMARD treatment n=153**	**Adjusted* OR**	**PsA-pregnancies with bDMARD treatment n=103**	**Adjusted* OR**
	n (%)	**n (%)**	**aOR* (95% CI)**	**n (%)**	**aOR* (95% CI)**
Preterm birth	417 (4.6)	7 (4.6)	1.08 (0.50-2.33)	18 (17.5)	**4.49 (2.60-7.79)**
Spontaneous onset	277 (3.0)	5 (3.3)	1.15 (0.46-2.85)	12 (11.7)	**4.73 (2.53-8.87)**
Medically indicated	140 (1.5)	2 (1.3)	-	6 (5.8)	**3.29 (1.28-8.46)**
Very preterm birth	61 (0.7)	0 (0.0)	-	0 (0.0)	-
Moderately preterm	356 (3.9)	7 (4.6)	1.21 (0.56-2.62)	18 (17.5)	**5.06 (2.91-8.79)**

*Adjustments were made for maternal age, country of birth, year of birth, parity, educational level, smoking status and BMI

5.3.4 Description of types of antirheumatic treatment during pregnancy

A more detailed description of type of antirheumatic treatment during pregnancy is presented in Figure 3. In summary, among the 153 pregnancies with non-bDMARD treatment, the majority, 128 pregnancies, had treatment with monotherapy (64 exclusively cDMARD and 64 exclusively corticosteroids) and 25 pregnancies had a combination of cDMARD and corticosteroids. Among the 103 pregnancies with bDMARD treatment, 46 pregnancies were treated with bDMARD as monotherapy, and 47 were treated with a combination of two types, either bDMARD and cDMARD (10) or a combination of bDMARD and corticosteroids (37). Ten pregnancies were identified with a combination of bDMARD, cDMARD and corticosteroids.

5.3.5 Analysis of preterm birth stratified on parity

Because there was an interaction between exposure status, i.e. PsA or non-PsA pregnancy, and parity when we analysed the outcome preterm birth, we stratified the analyses on parity in the different exposure groups based on presence and timing of antirheumatic treatment. Generally, we found increased risk of preterm birth in first PsA pregnancies compared to first non-PsA pregnancies. Among subsequent PsA births compared to non-PsA subsequent births, there was no difference regarding risk of preterm birth.

Figure 4. Proportions and adjusted ORs for preterm birth in matched (maternal age and year of birth) cohorts with respect to presence and timing of antirheumatic treatment comparing PsA pregnancies with non-PsA pregnancies stratified on parity. Adjustments were made for country of birth, smoking status, educational level and BMI.

	n preterm birth/N total pregnancies (%)		Adjusted OR* (95 % CI)
	Non-PsA pregnancies	PsA pregnancies	
PsA pregnancies (n=921)			
First	181/3390 (5.4)	45/339 (13.3)	2.50 (1.72-3.62)
Subsequent	263/5820 (4.1)	26/582 (4.8)	1.09 (0.70-1.71)
PsA pregnancies without treatment before and/or during pregnancy (n=495)			
First	99/1750 (5.7)	21/175 (12.1)	1.97 (1.15-3.38)
Subsequent	126/3200 (4.0)	14/320 (4.4)	1.06 (0.56-2.01)
PsA pregnancies with treatment before and/or during pregnancy (n=426)			
First	82/1640 (5.0)	24/164 (14.6)	3.14 (1.85-5.32)
Subsequent	110/2620 (4.2)	14/262 (5.4)	1.15 (0.61-2.17)
PsA pregnancies with treatment only before pregnancy (n=170)			
First	20/460 (4.4)	9/46(19.6)	3.95 (1.43-10.95)
Subsequent	54/1240 (4.4)	4/124(3.3)	-
PsA pregnancies with treatment during pregnancy (n=256)			
First	62/1180 (5.3)	15/118 (12.7)	2.92 (1.55-5.52)
Subsequent	56/1380 (4.1)	10/138 (7.3)	1.59 (0.73-3.45)

5.4 STUDY IV

5.4.1 Summary of main findings study IV

In this cohort study of 211 pregnancies with psoriatic arthritis, we found a numerical but not statistically significant difference in the proportion of pregnancies complicated by preterm birth in women with (vs. without) active PsA disease during the study period from one year before pregnancy until delivery.

5.4.2 Main results in study IV

Maternal characteristics, such as maternal age, smoking habits, educational level, BMI, calendar year of birth and parity did not differ between pregnancies with a registered moderate to high DAS28CRP value compared to pregnancies without. Neither was there a difference when the three subgroups of pregnancies were compared, i.e. pregnancies with a registered value of DAS28CRP during the study period (high-moderate or low) as well as pregnancies without a registration.

Thus, there was a difference in pattern of antirheumatic treatment. 31.7% of pregnancies without DAS28CRP registration did not use any antirheumatic treatment during the study period, compared with pregnancies with a registered moderate-high activity where 15% did not use any treatment and pregnancies with low activity where 10.9% did not use treatment. Comparing proportions of pregnancies that did not use any treatment between moderate-high activity and low activity did not differ Table 14. Further there was a corresponding difference in use of bDMARDs (Table 14).

Table 14. Proportions of anti-rheumatic treatment any time during the study period, comparing pregnancies with a registered moderate-high vs. low and none registered.

	PsA pregnancies with a registered DAS28CRP value ≥3.2 any time in the study period n=46	PsA pregnancies with all registered DAS28CRP values <3.2 any time in the study period n=64	PsA pregnancies with NO registered DAS28CRP values any time in the study period n=101	p-value*	p-value**
	n (%)	n (%)	n (%)		
No antirheumatic treatment	7 (15.2)	7 (10.9)	32 (31.7)	0.51	<0.05
Corticosteroids	22 (47.8)	24 (37.5)	40 (39.6)	0.29	0.53
cDMARD	23 (50.0)	28 (43.8)	35 (34.7)	0.52	0.18
bDMARD	34 (73.9)	46 (71.9)	32 (31.7)	0.81	<0.05

* P-values for differences between the two groups with available disease activity measures were performed with the use of Fisher's exact test.
** P-values for differences of categorical variables between the three groups were performed with the use of Chi square/Fisher's exact test depending on cell size

5.4.3 Disease activity and preterm birth

Due to low number of registrations during pregnancy, we collapsed the time strata into two time periods: i) any time during the time frame of the study and ii) in the year before start of pregnancy.

13% of the pregnancies with a registered moderate-high disease activity any time during the time frame of the study had a preterm birth compared to 7.8% among pregnancies with registered low disease activity and 7.9% among pregnancies without a registration. If HAQ was used as a measure of disease activity, 12.9% had preterm birth among pregnancies with a score ≥0.5 compared to 7.1% in pregnancies with low activity and 7.5% in those with no registration.

If the time frame was shifted to include just the year before pregnancy, 14.6% of the pregnancies with registered moderate-high disease activity had a preterm birth compared to 9.6% of pregnancies with a registered low disease activity and 6.8% of pregnancies without registration. When HAQ was used, 12.8% of pregnancies with a HAQ score >0.5 had a preterm birth compared to 10% of pregnancies with HAQ score ≤ 0.5 and 7.0% of pregnancies without registration.

None of the above described differences were statistically significant.

6 DISCUSSION

6.1 METHODOLOGICAL CONSIDERATIONS

6.1.1 Study design

To decide on appropriate study design is a balance between validity (the degree to which the information collected accurately answers the research question) and efficiency. A randomised control trial is the gold standard for analytic studies however, for many research questions a randomised control trial can be considered unethical or problematic (for example assignment of harmful exposures) why an observational design can be the best alternative. The cohort design is common in epidemiological studies and the Swedish population based registers provide a unique source of information for such studies.

In a cohort study, participants or study subjects are defined based on exposure. A cohort study can be prospective (participants are included before or at the time of exposure) or retrospective (the study begins after the exposure). In a retrospective design the risk of bias can be minimised if the information on exposure is recorded in a prospective manner *and* is registered independently of the outcome, this is common in register based cohort studies such as the studies included in this thesis. Cohort studies are well suited to study associations of rare exposures on specific outcomes, as the exposures included in the studies included in this thesis.

In **study I**, **II** and **III** we used the NPR, which has national coverage since 1987 for inpatient care and since 2001 for outpatient care, to identify exposure and with linkage to the MBR we had the opportunity to use pre-existing, prospectively collected information (i.e. information on BMI, smoking habits and country of birth) before the outcome (s) occurred. The MBR has almost full coverage of all births in Sweden since 1973. In **study IV** we identified exposure in SRQ and the outcomes in the MBR. A major limitation of register based cohort studies this is that information on exposure, outcome and potential confounders are restricted to information collected in the registers. A prospective cohort study with information collected for the purpose of the study would not have this limitation but would, taken the rare exposures in this thesis into account be, difficult to complete.

6.1.2 Systematic error

Systematic errors are non-random. They occur due to incorrect selection of study population, incorrect measurement of the studied variables or disregard for other factors that can influence the results (confounders). To increase sample size cannot affect systematic error.

6.1.3 Validity

The validity of a study consists of two components, i) internal validity which can be described as the extent to which the observed results represent the truth in the study population and ii) external validity which means generalisability of the findings to other populations. The major threats to internal validity are systematic errors (selection bias, information bias and confounding). If the internal validity is limited, the external validity will be affected as well.

6.1.4 Selection bias

Selection bias can be introduced if the association of exposure and outcome differs between those that participate in a study vs. the source population i.e. from the population from which the study population is sampled or recruited, this can lead to an under- or overestimation of the true association. Since both the NPR and the MBR are population based it limits the issue of selection, at least after 2001 when the outpatient component of the NPR became nationwide. In **study I** where information of exposure was collected during a long time period and started before the outpatient component of the NPR was nationwide there is a risk of a selection of more seriously ill study subjects who needed in patient care which could affect the outcomes studied. However we performed sensitivity analyses to explore this and it did not seem to affect the result. In **study I**, **II** and **III** we excluded pregnancies with systemic inflammatory diseases (from the study cohort) which is a selection but it affects the generalisability of the study more than the internal validity. Further, in **study I-IV** we included only singleton pregnancies limiting the generalisability to just singleton pregnancies. In **study I** and **III** we performed complete case analysis were pregnancies without full information on all variables were excluded from the analysis, if the pregnancies with missing information on variables are different than those with complete information this could introduce selection bias. In study **II** and **III** the population comparator pregnancies were initially sampled based on age and year at the index person's diagnosis and county of residence with the assumption that they were free from diagnosis of various chronic inflammatory arthritis diagnosis at the time the index person was diagnosed. They could theoretically develop a disease from that time point. We did not use the original matching in our studies but used all of the recruited population control subject with a registered birth in the MBR as a comparator cohort. These comparator pregnancies may be healthier than the source population and can thereby introduce a larger difference in the relation exposed/unexposed if this affects various pregnancy outcomes. Further, in **study IV** we used the SRQ for identification of subjects with PsA and for information of exposure, there may be a difference in registration of disease activity depending on disease duration and disease severity as well as type of treatment with less registration of pregnancies in remission for a long time or with a stable low activity but this is however a speculation.

Generally, when using the MBR there is a selection of pregnancies that complete 22+0 gestational weeks which is when inclusion in the MBR occurs. This may lead to undetected pregnancy complications that arises before this gestational length if there is an abortion before 22+0 gw. Complications arising early in pregnancy but with a birth >22+0 gw will however still be detected.

6.1.5 Information bias

Information bias occur when information about the exposure or the outcome of study subjects is systematically inaccurate, i.e. misclassified. Misclassification can be differential or non-differential depending on whether measurement error of one variable correlates with the measurement of another variable. When the misclassification is different in the exposed and non-exposed groups it is differential and leads to under- or over-estimation of the true association. Non-differential misclassification occurs equally in the exposed and unexposed groups and will typically lead to a dilution of the association of the exposure and outcome. In

study I we used one registered diagnosis in NPR but with requirement of a listing in rheumatology, internal medicine or paediatric departments to increase validity and decrease risk of misclassification of exposure. However, when we performed a sensitivity analysis with use of two separate visits or listings the point estimates were lower than in the original analysis and did not remain statistically significant in the subgroup JIA confined to childhood but did not affect the results in the subgroup JIA persisting into adulthood. This may indicate that we captured other conditions, more unspecific with only one diagnosis. Possibly these conditions should be closely related to JIA but not systemic inflammatory conditions which were excluded from the study cohort. Thus, misclassification of exposure in the subgroup JIA confined to childhood cannot be ruled out. In **study II** and **III** we used the criteria of at least two visits or listings with ICD-codes and at least one assigned from the department of rheumatology or internal medicine to reduce risk of misclassification of exposure. To date there are no validation studies of the diagnosis of PsA in the NPR. In **study IV** the risk of misclassification of exposure are most likely small due to the fact that the diagnosis registered in SRQ are assigned by the treating rheumatologist.

Many of the outcomes in all studies included in this thesis are data that are routinely collected during pregnancy and delivery and are not dependent on if the pregnancy is affected by JIA or PsA. However, a pregnancy in a woman with a chronic condition may be under more tight surveillance and thereby complications can be detected more often which can result in surveillance or detection bias. In Sweden, all women have free access to antenatal care and are offered regular visits during pregnancy. In **study I** where diagnosis of exposure is dependent on registrations before 18 years of age it may lead to an underreporting of childhood onset arthritis in women who immigrate to Sweden after 18 years of age and thus they will be misclassified as unexposed.

In **study III** we used information on antirheumatic treatment as a proxy for disease severity. The information about anti rheumatic treatment is based on dispensed prescriptions and for infusion of infliximab, information from SRQ. In **study III** we defined stratified groups based on treatment pattern. There may be women who collect their drug from the pharmacy but do not use it which leads to misclassification of exposure, disease severity and conclusions based on the treatment exposure may be wrong. On the other hand there may be women who have collected drugs at the pharmacy just before the study period started or, as with corticosteroids do have a supply at home to use in case of a flare. This will be undetected if not a new dispensation at the pharmacy is needed. Those pregnancies are misclassified as non-treated even though they use antirheumatic treatment. Misclassification of antirheumatic treatment in **study III** can be bi-directional i.e. both under- and overestimate the disease severity.

6.1.6 Confounding

A confounder is a variable that is associated with both the exposure and the outcome but is not an intermediate in the causal pathway. The concept of confounding implies that the effect of the studied exposure is distorted by effects of other variables-confounders which leads to a misrepresentative result. Unidentified confounders in a study may affect and alter the true association between an exposure and outcome. Risk factors for adverse pregnancy outcomes can, if they are unevenly distributed among the unexposed and exposed groups act as a

confounder but a risk factor is not a confounder by default. Confounding can be considered in the study design by randomisation, matching, stratification or restriction. In a large study population randomisation can reduce or eliminate both known and unknown confounders. Restriction is when you select study subjects with similar characteristics for variables that might be confounders but restriction in itself can introduce selection bias and affect external validity. Matching on variables that are potential confounders ensures an equal distribution of the variables among exposed and unexposed.

In the analysis of data both stratified analysis and adjustment in a multivariable regression model can be used to reduce confounding.

Many of the variables describing maternal characteristics in all of the studies included in this thesis can act as confounders and the information is mainly collected from the MBR. In **study I-III** maternal age, year of birth, maternal country of birth, educational level, smoking habits and BMI and parity were considered to be confounders

6.1.6.1 Maternal age

In **study I** the maternal age was younger among the exposed pregnancies than in the population comparator pregnancies and in **study II** and **III** the exposed women (pregnancies) were older than non-PsA women. Maternal age over 30 is associated with increased risks of preterm birth, stillbirth, caesarean deliveries and gestational diabetes (96-102). There are also studies indicating that young maternal age is associated with increased risk of various adverse outcomes (102-105). Maternal age is also related to parity why this has to be considered. Since maternal age was differently distributed among exposed and unexposed we treated this variable as a confounder and adjusted for this variable in the regression analyses in **study I-III** and matched on maternal age in the main analysis in **study III**.

6.1.6.2 Calendar year of birth

Calendar year can reflect changes in procedures in health care that is not dependent on the exposure or outcome under study as such but for example, the different versions of ICD-codes that is used to define exposure may capture the diagnosis differently. Also, indications for outcome procedures such as induction of labour and caesarean deliveries may change with time. Criteria for diagnoses can change, i.e. for gestational diabetes the criteria for diagnosis was changed in Sweden 2015. The new criteria used a lower glucose value as a threshold for diagnosis than earlier. This leads to increased number of pregnancies with a diagnosis of gestational diabetes. Also, the criteria for diagnosis of pre-eclampsia was changed in Sweden during 2019. This may alter the prevalence over time. Changes of definitions affects the possibility to compare risk of these outcomes over time. Prescription and treatment patterns for antirheumatic drugs and available antirheumatic treatments have changed over the study periods of the studies included in this thesis. In **study I** where time from start of exposure to outcome is many years, the women with JIA may have been treated in childhood and adolescence with antirheumatic drugs that nowadays would be considered suboptimal due to new and better treatment options of today. This may lead to a more active disease during longer time periods and consequently increased risk of joint destruction and secondary effects of active inflammation, especially if diagnosed and treated before bDMARDS were available. In **study I-III** there were differences in how the births in the

exposed compared to non-exposed pregnancies were distributed over the years. Calendar time, measured as year of birth, is considered a confounder in **study I-III**.

6.1.6.3 Maternal country of birth

There is more than one aspect of how country of birth can act as a confounder affecting the association between exposure and outcome. For several inflammatory diseases a genetic predisposition and an environmental trigger are of importance for the risk of developing the diseases. The incidence of arthritis diseases varies in different parts of the world and most incidence studies have focused on RA, the most common chronic inflammatory arthritis disease. In the northern part of the world, incidence rates for RA are generally higher than in the southern part (106). In **study I-III** exposed women were more often born in the Nordic countries than unexposed. Further, immigrant women in Sweden have increased risk of preterm birth compared to Swedish born comparators (107). Immigrant women from sub-Saharan Africa, Latin America and the Caribbean are also reported to have an increased risk of pre-eclampsia compared to native born women in different industrialised countries including Sweden (108). We adjusted for country of birth, categorised into Nordic and Non-Nordic, in **study I-III**.

6.1.6.4 Educational level

Highest level of attained education, categorised into ≤12 years or >12 years of education, was used as a proxy of socio-economic status in the studies included in this thesis. There are some evidence that JIA may affect highest attained level of education (109), may risk to affect school attendance (110) and that a diagnosis of chronic inflammatory arthritis affects working life (111-113). Low educational level and low socio-economic status, measured in different ways, are associated with adverse pregnancy outcomes (114-118). In the Swedish National Board of Health and Welfare's yearly report from December 2020, maternal age-standardised characteristics and selected delivery outcomes are presented by attained educational level (119). The report indicates a relationship between attained educational level and smoking as well as with overweight and obesity. A lower proportion, 0.8%, are smokers among women with more than 12 years of education as compared to 11.9% smokers among women with 9 years of education. In women with the highest level of education the proportion of obesity was 11.4% and in the group with lowest education 25.7%.

Adjustments for educational level were performed in **study I-III.**

6.1.6.5 Smoking habits

Smoking during pregnancy is associated with adverse pregnancy outcomes (foetal growth restriction, preterm birth, placental abruption and stillbirth) (120, 121). The proportion of women who report that they were smokers at first antenatal visit during pregnancy have dramatically decreased during the last 20 years (122). In 1992, the first year of the study period in **study I**, 22.9% were smokers at the first antenatal visit and in 2017, the last year of the study period in **study III**, 4.6% were reported as smokers (122). Smoking is a risk factor for RA (123) but have a more uncertain role in PsA, it seems that smokers in the general population have an increased risk to develop PsA compared to non-smokers but smokers among persons with psoriasis seem to have a decreased risk to develop PsA compared to non-

smokers (124). However, in **study I-III** there were more smokers in the exposed group compared to the unexposed. We adjusted for smoking status in **study I-III**.

6.1.6.6 BMI

Both maternal underweight (BMI <18.5) and overweight (BMI 25.0-29.9) as well as obesity (BMI >30) have been reported to be associated with preterm birth (125, 126). Overweight and obesity is also associated with increased risk for post term birth (125). Obesity is associated with gestational diabetes (127), gestational hypertension and pre-eclampsia (128-130), LGA birth (131, 132), stillbirth and infant death (133-135). In addition, obesity is associated with caesarean delivery (136-138). Among birthing women in Sweden obesity and overweight are associated with country of birth and socioeconomic factors where women with lower level of education have increased risk of obesity (139).

In **study I-III** there were differences of BMI distributions between exposed and unexposed groups. We adjusted for BMI in **study I-III** but also modelled effect of exposure on outcomes without BMI adjustment in **study II**.

6.1.6.7 Parity

Parity is a description of the number of pregnancies that have passed beyond the gestational age of viability at birth, live or stillbirth.

Generally, women with inflammatory diseases are reported to have reduced fertility but the reason for this is most likely multifactorial and includes factors as disease activity, use of antirheumatic drugs and psychological factors (140-143). In a population based Norwegian study of births 1967-1995, published in 2001 the authors report increased maternal mean age at first birth, and lower mean age in subsequent births indicating a shorter reproductive period. This finding was however altered by time period of the study, with increased subsequent pregnancy rate with time (144).

For all women, irrespectively of rheumatic disease, there are data indicating that adverse pregnancy outcomes can affect decisions about future pregnancies. For example, in a population cohort study of singleton pregnancies in Norway with births 1967-1996 the association of mode of delivery and the probability to have a future birth was dependent on infant survival the first year after birth. If the infant was stillborn or died there was no association between mode of delivery and chance of a future birth. If there was a live born infant there was a lower rate of women that had a future birth after caesarean delivery in all maternal age groups, among low-risk pregnancies and in subgroups with pre-eclampsia and breech presentation (145).

In the general birthing population, there is a described recurrence risk of for pre-eclampsia (146, 147), SGA birth (148-150) and preterm birth (151-153), conditions that are to some extent interrelated. A pregnancy and delivery after a first caesarean birth is associated with more complications compared to a first vaginal birth (154-157).

A population based study from Norway showed that adverse pregnancy outcomes such as pre-eclampsia, SGA birth and preterm birth had a higher recurrence rate in women with

rheumatic diseases (including connective tissue diseases, RA, JIA AS and non-specified inflammatory arthritis diseases) as compared to women without rheumatic diseases (158). Further there are studies that report increased adverse pregnancy outcomes associated with first birth after diagnosis of inflammatory joint disease (4) but not subsequent, and greater differences in first births than subsequent (15).

In **study I** we adjusted for parity in the analyses, in **study II** and **III** we both adjusted and stratified for parity in the analyses and in **study III** we matched when we assembled the study cohort.

6.1.6.8 Residual confounding

Residual confounding is confounding that remains after controlling for confounding in the design or /and analyses in a study. There are several reasons for residual confounding where one is the existence of confounding factors that were not considered either due to lack of data for these factors or that no attempt was done to adjust for them. Other reasons for residual confounding are that the control is not enough to reduce the total effect of the confounder or measurement errors in the confounding variables. Unmeasured maternal factors and residual confounding might be present in all studies included in this thesis.

6.1.6.9 Confounding by indication

Confounding by indication or channelling bias arises when subjects who receives an intervention or drug are inherently different from those who do. In **study IV** in which the exposure was a registered value of disease activity is the exposure we kept pregnancies without the registered measure for comparison in the study since we hypothesised that increased disease activity, a more severe disease or treatment with bDMARD might affect the possibility of having a registration in SRQ and at the same time these factors are associated to the outcome under study.

6.1.7 External validity

In **study I** the study cohort comprises all births in the MBR during the study period and are population based and nationwide as well as the NPR which was used for identification of exposure. However only singleton pregnancies were included in **study I** as well as in **study II-IV** which influences the generalisability to multiple births. In **study II**, the included pregnancies were diagnosed with PsA before their first birth which also may influence generalisability of these results to subsequent births after diagnosis. The results from all the studies in this thesis may not be generalizable to other populations with different accessibility of maternity care.

6.1.8 Random error

Random error refers to variability in data that is due to chance. It can be reduced by increased sample size and thereby increase precision. Statistical techniques such as p-values and confidence intervals can be used to quantify the degree of precision in the observed estimates. In this thesis the confidence levels were set to 95% in **study I-III.** Several of the pregnancy and delivery outcomes of interest are rare i.e. pre-eclampsia and preterm birth and so even if the underlying cohort size was large the precision was somewhat hampered in **study II** and

III. In **study IV** we may have seen a difference in risk of preterm birth when we compared pregnancies with moderate-high active PsA with low active PsA if the size of the study cohort had been larger.

6.2 FINDINGS AND IMPLICATIONS

The main exposures studied in the work included this thesis, JIA and PsA, are each captured by only a few ICD codes, although the diagnosis and underlying diseases themselves are multifaceted and defined more by the relationship of the condition as contrasted to other conditions than by a specific set of symptoms. As such, they are "entities" rather than distinct diagnoses with symptoms and presentation changing with a patient's age and over time. For these reasons, it became apparent that studying these exposures involved a great deal of complexity. Nevertheless, given the sparsity of studies addressing these conditions' effects on pregnancy available when the work with this thesis started, I think it is important to address these conditions.

6.2.1 Inflammation and time

In **study I**, we studied the effects of a history of a diagnosis of arthritis before 18 years of age in relation to pregnancy outcomes. We found two distinct patterns of inpatient and outpatient visits. We defined two groups based on these patterns: JIA pediatric only and JIA persisting into adulthood. In each of these groups, there may be a different distribution of JIA subgroups, but we were not able to study this. JIA is not one disease, and the subgroups each have different features and underlying pathology (40). Thus, a Swedish longitudinal study of JIA patients concluded that there was a "considerable and continuous change in JIA categories during the study period", (159) why this may be of less importance.

We found differences in the two subgroups. JIA paediatric only consisted of the majority of JIA pregnancies. Even though we considered these pregnancies to lack actual or recent inflammatory activity, we found increased odds of preterm delivery, moderately preterm delivery and medically indicated delivery. Further, induction of labour was more common among JIA paediatric pregnancies vs. population pregnancies, and the aORs for caesarean delivery, both emergency and elective, were increased. In an analysis of proportions of pre-eclampsia by adverse outcomes, there was no explanation of the adverse outcomes from diagnosis of pre-eclampsia in the JIA paediatric group. This may be due to residual effects of past inflammation, which may affect endothelial function and the structure of vessels; (160-162), this however remains a speculation. Diagnosis of JIA persisting into adulthood was associated with an increased risk of pre-eclampsia, preterm birth and SGA birth. All of these outcomes may be related. Unfortunately, the indications of induction of labour and caesarean delivery are not entered into the MBR in such a way as to provide a variable for study. This is an aspect of register studies that needs to be considered. However, even though we do not know about antirheumatic treatment or disease activity during pregnancy, we can clearly demonstrate that a diagnosis of JIA with ongoing course into adulthood is associated with increased risk of adverse pregnancy outcomes. The presence of pre-eclampsia seems to be the major driver for other adverse outcomes, judging by the proportions of pre-eclampsia among JIA in comparison with population pregnancies in selected adverse outcomes. Of the preterm births in JIA persisting into adulthood, 22.9% also had a diagnosis of pre-eclampsia,

compared to 12.4% in population comparator births. Among the medically indicated preterm births in JIA persisting, 45.5% had a diagnosis of pre-eclampsia compared to 36.6% in population comparator births. In SGA births, 32.1% in JIA had a diagnosis of pre-eclampsia vs. 14.3% in population comparator births. The differences in caesarean deliveries were not striking.

Pre-eclampsia has earlier been characterised by abnormal placentation and endothelial dysfunction, with early onset pre-eclampsia being characterised by defect placentation and late onset pre-eclampsia more affected by maternal metabolic factors such as diabetes (163). New evidence suggests that the maternal cardiovascular system in itself plays a role in the pathogenesis of pre-eclampsia (164). Individuals with rheumatic diseases have an increased risk of CVD, thought to be caused in part by elevated levels of factors such as circulating pro-inflammatory cytokines, circulating autoantibodies and specific T cell subsets. Taken together, this is believed to drive the increased CVD risk by promoting the formation of atherosclerotic plaques and cardiovascular remodelling (165).

Given the results of this study with increased risk of early onset and late onset pre-eclampsia, SGA birth, and spontaneous as well as medically indicated preterm birth and of very as well as moderately preterm birth in JIA persisting into adulthood, I suggest that we consider low dose aspirin to this group of women as prophylaxis for pre-eclampsia.

6.2.2 Psoriatic arthritis and pregnancy outcomes

In **studies II**, **III** and **IV**, the exposure variable includes diagnosis of PsA.

In **study II**, we found that diagnosis of PsA was interrelated with obesity and smoking, as well as with other rheumatic co-morbidities and with IBD. The previously published studies about PsA and pregnancy outcomes at the time of conduction of our study were small. For example, they did not include any information on BMI. One of the studies published, a Danish-Swedish population based cohort study of Pso and PsA, reported similar maternal characteristics as ours among the 964 studied PsA pregnancies. Their study cohort consisted of approximately 2/3 subsequent births. 13% were smokers, 17% had a BMI >30 and 14% had diagnosis of RA. In conclusion, their study cohort was similar to ours, except regarding parity. In our cohort, approximately 50% of the exposed pregnancies were overweight or obese, 60% were first pregnancies, and 5.9% had a diagnosis of RA. We considered our cohort to be representative of PsA pregnancies in the Nordic countries at least.

When we modeled our regression model, we abstained from adjusting for BMI in one of the analyses and included BMI as a confounder in the fully adjusted model. This was because of an uncertainty about how to handle obesity in relation to PsA, i.e. whether it should be considered as "a part of the entity" or if the arthritis disease in itself could cause obesity via for example physical inactivity. Obesity is described as an important co-morbidity in PsA, and is also a risk factor for developing psoriasis in the general population. Data further support that the prevalence of obesity increases when the severity of psoriasis increases (94). The association of PsA with obesity may be described as bi-directional, as illustrated by studies indicating that weight gain can be a consequence of decreased physical activity in persons with joint dysfunction. Obesity is concomitant with an ongoing low grade of inflammation. Studies indicate an increase in many cytokines as well as interleukin (IL)-17

and IL-23 plasma levels in obese women compared with lean individuals. A higher risk of developing obesity in PsA patients may be due to common pathophysiological mechanisms (166, 167).

In the analyses comparing outcomes in PsA vs. non-PsA pregnancies, the effect of also including BMI as a confounder was generally minor, why we interpreted our results as an effect of PsA and not of obesity alone.

In the main analysis of outcomes in PsA pregnancies compared to non-PsA pregnancies, we noted increased aORs of preterm birth, spontaneous preterm birth, medically indicated preterm birth and moderately preterm birth. There was also an increased risk of caesarean delivery, both by the overall estimate and when stratified as elective. When we stratified the analysis by parity, the risk of preterm birth was further attenuated among first pregnancies but was not present in subsequent births. The increased risk of caesarean delivery was intact among subsequent births, and now also significant for the strata of emergency caesareans. An interesting finding among the subsequent births was an increased point estimate of pre-eclampsia, however this was not statistically significant. aOR for pre-eclampsia in the main analysis of PsA vs. non-PsA was 1.21, 95% CI 0.78-1.88 in the fully adjusted model. Among subsequent pregnancies, aOR in the fully adjusted model was 1.77, 95% CI 0.77-4.11. The proportion of pregnancies with pre-eclampsia was very low, namely 2.8% among PsA pregnancies vs. 1.5% in non-PsA pregnancies.

After an analysis in a restricted cohort with exclusion of pregnancies with co-morbidities before pregnancy, the estimates of preterm birth overall and caesarean delivery remained increased.

We interpreted the main result of a higher risk of preterm birth as originating from exposure to PsA. In this study of PsA, **study II**, there was no risk of pre-eclampsia nor SGA. The large difference in outcomes compared to our study of JIA is challenging. In **study II**, we did not have information on disease activity or antirheumatic treatment. This was also true for the JIA study, **study I**, but there, we had an indication that patients had lived for a presumably long time with a chronic inflammatory disease. In the study by Bröms, pregnancies with PsA had an increased risk of gestational hypertension and pre-eclampsia but not of SGA birth (72).

In **study III**, we wanted to assess disease severity by the proxy of antirheumatic treatment, under the hypothesis that an antirheumatic treatment with more than one drug or treatment with bDMARD during pregnancy is an indicator of a more severe disease than a pregnancy without antirheumatic treatment. We further hypothesised that there may be decisions and changes in antirheumatic treatment in the year preceding a pregnancy that we do not capture if we were to assess only antirheumatic treatment pattern during pregnancy.

In the Swedish guidelines from SRF regarding anti-inflammatory and immune modulating treatment during pregnancy and breastfeeding, the general advice is to plan a pregnancy to a period with low disease activity or remission. The current advice regarding TNFi is to stop treatment if disease is in remission or at a low activity. For women with moderate to high disease activity, treatment with selected TNFi:s can continue, but an evaluation before gestational week 30 is suggested. This advice is due to the increased transport of antibodies

(IgG1) over placenta, predominantly during the third trimester. If there is a strong indication, the treatment can continue. The best studied bDMARDs during pregnancy are certolizumab pegol and adalimumab and they are approved by the European Medicines Agency, EMA, for use during pregnancy. Treatment with certolizumab pegol (no Fc part) and etanercept (soluble TNF-receptor) results in less transport of the drug over the placenta, compared to substances with complete IgG1 (infliximab, adalimumab and golimumab) (168). In **study III**, we collapsed TNFi and other biologic treatments into "bDMARD" for simplicity, and categorised treatment further in cDMARD for conventional DMARDs and CS for corticosteroids.

In **study III**, we studied the exposure of PsA stratified on presence, timing and type of anti-rheumatic treatment. However, in the main analysis, before stratification there were increased risks of preterm births and caesarean deliveries but not of pre-eclampsia, SGA or LGA birth.

Interestingly, among pregnancies without any dispensed antirheumatic treatment one year before pregnancy until delivery, there were increased risks of medically indicated preterm birth and elective caesarean delivery compared to non-PsA pregnancies. The stratified analyses differed by timing of treatment with the most increased risks in pregnancies with treatment during pregnancy, especially bDMARD treatment. We noted the most increased risks in PsA pregnancies with bDMARD treatment during pregnancy. Among those pregnancies, there was an increased risk of pre-eclampsia, aOR 2.88, 95% CI 1.35-6.16, as well as increased risks of preterm birth, spontaneous preterm birth and moderately preterm birth as compared to non-PsA pregnancies. We interpret this as meaning that those pregnancies have an indication to continue, or start, with antirheumatic treatment during pregnancy based on a presumably more severe disease than a pregnancy without treatment. However, from clinical experience, we know that women may abstain from treatment even though they have an indication, due to a fear of complications from the drug itself.

In a systematic review and meta-analysis of bDMARD treatment before and during pregnancy in women with chronic inflammatory arthritis and IBD, (169) there was no association between use of bDMARD during pregnancy and risk of preterm birth compared to non-bDMARD exposed disease comparators. A population based study of pregnant women with various inflammatory diseases (IBD, RA, AS, PsA, and Pso) reported adverse pregnancy outcomes in women treated with TNFi compared to women with non-biologic systemic treatment (170). The authors concluded that the diverse findings across disease groups may indicate an association related to the underlying disease activity, rather than agent-specific effects.

Preterm birth is a complex outcome which is important to recognise, because it is a leading cause of morbidity and mortality in the neonate (171-173). When studying preterm birth, it is important to investigate or assess different reasons for the onset of preterm birth, because they may reflect different underlying causes. There are studies indicating a genetic pre disposition for preterm birth (174, 175) and hereditary factors are described to be involved in approximately 25% of the cases (173). Cytokines, such as interleukin-1 (IL1), IL6, IL8, and TNFα, plays a role in preterm birth, (174, 176) as well as in chronic arthritis diseases (78, 177). A genetic overlap has been suggested between IBD and preterm birth (174) but there

are no such publications, to my knowledge, for genetic overlap in chronic inflammatory arthritis diseases and preterm birth.

Spontaneous preterm birth, defined as spontaneous onset labour with contractions or premature pre-labour rupture of membranes and birth before 37 gw, most likely has a multi-factorial underlying cause (171, 178, 179). Several factors have been linked to increased risk of spontaneous preterm birth: previous preterm birth (180), maternal overweight and obesity (126), underweight (181), diabetes (182, 183), and smoking (184), among others. An association between spontaneous preterm birth and RA and other autoimmune diseases has been reported earlier (10, 185).

In **study III**, we found that the risk of spontaneous preterm birth ranged from being comparable to that for non-PsA pregnancies among pregnancies without any antirheumatic treatment to showing a fourfold increased risk in pregnancies with bDMARD treatment during pregnancy. These findings strengthened our hypothesis that disease severity has an impact on risk, at least with regard to spontaneous onset preterm birth.

In contrast, medically indicated preterm birth reflects pregnancy complications, but is also influenced by obstetric management. As such, stratifying by parity can be a way of assessing this. An interesting publication addresses the mediation of adverse outcomes, for example preterm birth and cesarean delivery, in autoimmune diseases. The strongest mediator for preterm birth in pregnancies with RA, SLE and psoriasis was pre-eclampsia/hypertensive disease, accounting for 20-33% of excess risk (186). This may be what we noted in **study I**, even though we did not perform a mediation analysis.

There is sparse knowledge of the effect of disease activity on preterm birth in PsA pregnancies (77). Disease activity flares and increased disease activity during pregnancy have been associated with preterm birth in studies of other rheumatic diseases such as SLE (187), RA (27, 39, 188) axial spondyloarthritis (188), and JIA, (39) so this scenario seems plausible. We therefore conducted study IV, in which diagnosis of PsA was defined according to the treating rheumatologist entering data into the SRQ. In the cohort of PsA pregnancies, we used values of DAS28CRP and HAQ as exposure, defining a DAS28CRP <3.2 as low disease activity and a value of DAS28CRP ≥3.2 as moderate to high. A HAQ score of >0.5 was here considered as active PsA disease. We used the time frame from one year before pregnancy until birth as the study period for each pregnancy, the time period was divided into seven strata. The study was unfortunately hampered by the availability of few registered values during pregnancy and hence, the proportions are imprecise. In any event, this is an important finding as such. We used the best possible data from a decade of pregnancies, and the data were still sparse. This is not exclusive to this study. Ursin et al. (76) included 108 PsA pregnancies in a study of disease activity during and after pregnancy 2006-2017. Only 38 (35%) of the pregnancies had a pre conception visit and 32 of the 38 (84%) of these pregnancies had a registered value of DAS28CRP. The time frame for the pre conception visit in the study was any time one year before pregnancy. However, during the study period there were increased rates of both visits and registered values of DAS28CRP.

A study of pregnancy outcomes in DMARD treated women with JIA from Germany included 152 pregnancies with JIA 2007-2018. It was based on data from a JIA biologic register in

combination with a follow up register- both these German registers are described as multicenter prospective observational cohort studies. Patients were assessed every 6 months of a rheumatologist and patient reported outcomes were routinely evaluated every 6 months. Physician and patient reports within 12 months before, during and up to 6 months after pregnancy were included in the analyses. Patients were also asked to participate in a structured interview early in pregnancy and 6 months after delivery. The authors describe that on average there was 1.6 physician and 3.0 patient reports available from the study period (12 months before pregnancy, during and until 6 months after delivery). In the analyses, missing values for clinical Juvenile Arthritis DAS-10 were imputed.

To conclude: our studies indicate that in general a PsA pregnancy is associated with increased risk of preterm delivery and caesarean delivery compared to non-PsA pregnancies. These associations do not seem to be due the unfavorable maternal characteristics that are more frequent in PsA pregnancies and also risk factors for preterm birth.

Parity influences risk of preterm birth in PsA pregnancies compared to non-PsA pregnancies and the association is mainly confined to first pregnancies. The reason for this however remains unclear.

Further, when antirheumatic treatment is used as a proxy for disease severity PsA pregnancies considered to have the most severe disease with ongoing bDMARD treatment during pregnancy also exhibits the most severe adverse outcomes compared to non PsA pregnancies.

Disease activity in PsA pregnancies may be associated to preterm birth, we noted numerical differences in proportion of preterm in moderate-high active vs. low active PsA. The study was hampered by sparse data and low precision. This question needs to be further evaluated in a prospective manner in the future.

The findings in **studies II** and **III** implies that first pregnancies, especially in women with bDMARD treatment during pregnancy should be surveilled during pregnancy.

7 CONCLUSIONS

i) Pregnancies in women with JIA have increased risks for adverse outcomes including pre-eclampsia, SGA birth, preterm birth and ceaserean delivery.

ii) Pregnancies in women with PsA have increased risks for preterm birth and caesarean delivery.

iii) Even though women with PsA have more co-morbidities, are more obese and more often smoke than women without such a diagnosis, the adverse pregnancy outcomes are not due solely because of these factors.

iv) Parity influences risk of preterm birth in PsA pregnancies and the increased risk is predominantly seen in first births.

v) When antirheumatic treatment is used as a proxy for PsA disease severity, the most increased adverse outcomes, compared to pregnancies without PsA, are seen in pregnancies with the most severe disease.

8 POINTS OF PERSPECTIVE

Based on the findings in study I-IV the following questions are raised

i) *What instrument should be used to measure disease activity during pregnancy?*

ii) *When is it valuable to assess disease activity during pregnancy?*

iii) *How do we assess, in a prospective and detailed way, what antirheumatic treatment that is actually used?*

iv) *What are the indications of caesarean deliveries and induction of labour?*

v) *Can we by increased surveillance during pregnancy improve outcomes?*

vi) *What do pregnant women want to know?*

9 ACKNOWLEDGEMENTS

Throughout this education I have received endless support, help and inspiration from so many of you through both clinical and scientific work. I would like to express my genuine gratitude to all who have supported me. Especially, I would like to thank:

Olof Stephansson, my main supervisor, for introducing me to this area of research and for sharing your huge knowledge of perinatal epidemiology. You always convey enthusiasm and curiosity and get things done. That is inspiring. You have had an immense patience, which by far exceeds what can be expected, with me and with all subgroups, sensitivity analyses and different exposures. Thank you for believing in me during all these years.

Johan Askling, my co-supervisor, for sharing your scientific thinking, expertise in epidemiology and ability to disentangle and clarify even the most blurry sentences. I also appreciate your kindness.

Kari Johansson, my co-supervisor, for your humble expertise in so many areas and because you are always thinking about what's best for me. Thank you also for magically managing to structure both my thoughts and manuscripts. You have been important to me during this time and you mean a lot to me.

Karin Hellgren, my co-supervisor and last to join the growing team of supervisors for this thesis work. I am truly happy that you did. Without your expertise in this area it wouldn't be possible to have come this far. Apart from that, I have really enjoyed our talks, about other important things in life. Thank you for being patient, always kind and that you look after my best.

Fredrik Granath, my co-author, for more than can be expressed in a few lines. Your expertise as a biostatistician in combination with a unique competence regarding pregnancy cohorts have been invaluable to me. Thank you also for always taking the time to listen to me, to discuss with me and explain things over and over again in different ways. You are a real scientist.

The entire "**REP-KEP**" **group**, for being the best possible group and for the discussions which always are interesting, supportive and inclusive. **Olof,** for steering this at present and to **Sven Cnattingius** who did it earlier. It has been fun to be a little part of this dynamic group.
Anna Sandström and **Mia Ahlberg,** my co-workers and dear friends, for being there for me, for scientific discussions and not so scientific discussions, for laughter and passion, for support and for everything. **Louise Lundborg** and **Linnea Ladfors,** fellow doctoral students and friends, for your enthusiasm, energy and for all your support. I will miss being a part of the doctoral student gang.

Michael Fored, director of research education, for support in all moments of despair and for a robust belief in my ability to complete this education.

Johan Askling (current) and **Anders Ekbom** (former), head of the Division of Clinical Epidemiology, for creating a fantastic research environment with the best possible conditions to conduct register based research. **All co-workers** at KEP for invaluable support and so much fun during the years, including interesting lunch and fika sessions. An extra thank you to **Eva Willis** and **Helena Nord** for always being kind, helpful and interested in me and my research. **Pernilla Appelquist** for being you, for sharing life hacks and for being lion-hearted when it comes to tackling administrative obstacles. **Samir Hussin** and **Farzad Hedayaty** for excellent support regarding IT-matters (interpreted in its broadest sense, including encouragement and the "everything will be alright-attitude").

All past and present doctoral students at KEP, (it's not possible to mention everyone by name considering the time I have spent with completing this thesis) for interesting discussions and company. An extra thank you to **Arvid**, **Elsa**, **Fredrik**, **John**, **Hjalmar**, **Renata**, **Andrei**, **Marios**, **Henrik**, **Huiling**, **Kristin** and **Peter** for nice company in the doctoral students' room.

Anders Carlsson, my mentor, for support in the beginning of the work with this thesis.

Berith Karlsson Tingåker, my former clinical mentor and colleague, for encouragement, many years of support and friendship.

All former heads of the Department of Obstetrics and Gynecology at Karolinska University Hospital for support during the years I worked there. **Katarina Bremme**, **Eva Nord,** and **Maria Sennström** for sharing your clinical expertise and for everything you taught me about the clinical management of rheumatic conditions during pregnancy. In addition, I want to express my gratitude for the support I received from **Karin**, **Åsa, Bibbi** and **Merja** working as midvives at the specialist antenatal care and from **Barbro** and **Kajsa** at C23. You all conveyed knowledge and memories for life.

All former colleagues and friends at "kvinnokliniken" Karolinska universitetssjukhuset Solna, for sharing your knowledge and for the fun.

Sophie Graner (current) and **Ann Hjelm** (former), head of BB Stockholm, for your inexhaustible support and for creating a generous, inspiring and positive work environment.

Ingela Wiklund, CEO and **Britta Wernolf** care manager of BB Stockholm, for encouraging research, for interest, for having created a clinical environment where research and research questions are important.

My fabulous, generous and absolutely outstanding co-workers at BB Stockholm. I am truly grateful for your support and encouragement. It is a favour to be surrounded by you at the clinic. **Lena, Susanne and Ann**- it is 20 years since you inspired me to be an obstetrician and a researcher. It took some time but I am eternally grateful to you for taking me on. **Malin**, **Camilla**, **Elaine**, **Linn**, **Louise**, **Anna**, **Magdalena**, **Git**, **Barbara**, **Karin**, **Sophie** and **Charlotte** for encouragement and support. I'm happy to be a part of this group.

Karin Eriksson, my dear friend and colleague, for your loyal faith in me, your kindness and for the fun working as Bill och Bull.

Charlotte Iacobaeus, my dear friend and colleague, for being my biggest supporter, for coaching, for always finding a solution, for your razor sharp analyses of scientific as well as everyday matters.

Cuckoo's Nest, for your unconditional support and belief in me.

Lotta Lindblad Wollman, **Ingela Hulthén Varli**, **Malin Holzmann**, **Ingrid Sääv** and **Sophie Graner,** friends and colleagues, for support, encouragement and sharing both ups and downs for many years.

Tekla Lind and **Ameli Norling,** friends and colleagues, for your belief in me, for support, laughter and for the joy of being close to two super-brains.

Anna Z, my friend, for keeping me sane, for friendship and support. **Annika** and **Lena**, my sisters and their families, for creating togetherness and support.
My parents, **Ann** and **Bertil**, for endless support and always believing in my ability to complete this education.

Simon och **Sara**, mina älskade barn, ni är bara bäst!

Niklas, my beloved husband, for your endless support and belief in my abilities. For encouragement, interest in my research and patience with me when I don't realise that PsA isn't the centre of the universe. For linguistic excellence and for helping me out with whatever I need whenever I need it. I love you.

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